Official Title of Study:

A Phase 1, Open-label, Dose Finding Study of CC-90009, a Novel Cereblon E3 Ligase Modulating Drug, in Subjects With Relapsed or Refractory Acute Myeloid Leukemia or Relapsed or Refractory Higher-Risk Myelodysplastic Syndromes

NCT Number: NCT02848001

Document Date (Date in which document was last revised): 31 Mar 2022

A PHASE 1, OPEN-LABEL, DOSE-FINDING STUDY OF CC-90009, A NOVEL CEREBLON E3 LIGASE MODULATING DRUG, IN SUBJECTS WITH RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA OR RELAPSED OR REFRACTORY HIGHER-RISK MYELODYSPLASTIC SYNDROMES

PROTOCOL NUMBER:	**CC-90009-AML-001**
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EudraCT NUMBER:	**2017-001535-39**
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SPONSOR NAME/ ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}

Signature of Celgene Therapeutic Area Head **dd mmm yyyy**

[redacted]

Printed Name of Celgene Therapeutic Area Head and Title

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

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Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:**_____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 9:

The main purpose of this amendment is to provide mitigation strategies for the risk of serious and fatal infections with CC-90009 that was observed in the initial subjects in the Part B Dose Expansion.

Significant changes included in this amendment are summarized below:

- Modification of CC-90009 dose and schedule for Part B Dose Expansion
- Addition of dose modifications for concomitant use of strong CYP3A4 inhibitors in Part B Dose Expansion

The amendment also includes other minor clarifications and corrections:

- Update of prior clinical experience with CC-90009 to align with the most current version of CC-90009 Investigator's Brochure, Edition 8.0 (Section 1.2.3 Prior Clinical Experience with CC-90009).
- Update of requirement of dexamethasone premedication for Days 1-7 schedule in Section 1.2.4 Safety Monitoring Plan, Section 7.2 Treatment Administration and Schedule, and Section 8.3 Required Concomitant Medications and Procedures.
- Update of study duration based on current study status in Protocol Summary and Section 3.2 Study Duration for Subjects.
- Addition of safety follow-up of all adverse events/serious adverse events associated with confirmed or suspected severe acute respiratory syndrome coronavirus 2 infection in Section 6.3.1 Safety Follow-up.
- Exclusion of subjects from efficacy long term follow-up when new anti-cancer therapies are initiated in Section 6.3.2 Efficacy Long Term Follow-up
- Tables for Part A and Part B cohort at 3.6 mg Days 1-5 blood pharmacokinetic sampling schedules were moved from Section 6.5.1 to new Appendix Q.
- The study will implement an updated CC-90009 Pregnancy Prevention Plan in Appendix L.

Additional revisions, including to sections of the Protocol Summary, have been made to align the protocol with respect to these changes. Other clarifications, corrections of minor typographical errors and incidental formatting changes were made throughout the document.

This protocol amendment applies to all subjects.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 9		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.2.3.1: Study CC-90009-AML-001 Section 1.3.4: Rationale for Dose and Dosing	• Added details of closure for initial Part B cohort at 3.6 mg Days 1-5 and addition of the 2 new cohorts at 2.4 mg Days 1-7	A high rate of sepsis was observed in subjects enrolled in the initial Part B cohorts. Comprehensive analysis of available pharmacokinetics,

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 9		
Section Number & Title	**Description of Change**	**Brief Rationale**
Schedule in Part B Dose Expansion Section 3.1: Study Design Figure 4: High Level Study Design Section 4.1: Number of Subjects Section 7.2.8: Definition of Stopping Criteria Section 9.9.3: Stopping Rules Regarding Toxicity in Part B Dose Expansion Appendix P	and 3.0 mg Days 1-7 (updated in Section 1.2.3.1, Section 1.3.4, Section 3.1, Figure 4, and Section 4.1). • Added details of the non-binding Bayesian method that will be utilized to monitor excess toxicities in Part B (updated in Section 3.1, Figure 4, Section 7.2.8 and included in new Section 9.9.3 and new Appendix P). • Added details for Safety Review Committee (SRC) assessment of new doses and schedules for subjects enrolled in new cohorts in Part B (updated in Section 3.1, Figure 4, Section 7.2.8 and included in new Section 9.9.3).	pharmacodynamics, efficacy, safety, and tolerability data were used to select the new doses and schedule for evaluation as part of a strategy to reduce the risk of sepsis. The SRC will continue to assess the tolerability of the doses and schedule used in Part B as described in the protocol and the expanded cohorts will be monitored for the excess toxicities, including sepsis, utilizing the non-binding Bayesian stopping criterion on a continuous basis.
Section 1.2.3.1: Study CC-90009-AML-001 Section 1.2.4: Safety Monitoring Plan Section 1.3.4: Rationale for Dose and Dosing Schedule in Part B Dose Expansion Section 7.2.15: Dosage Modifications for Concomitant Use of Strong CYP3A4 Inhibitors in Part B Dose Expansion Section 8.2: Prohibited Concomitant Medications and Procedures	• Added exposure data for subjects who received strong CYP3A4 inhibitors (Section 1.2.3.1 and Section 1.3.4) • Added text for potential drug-drug interaction (DDI) with strong inhibitors of CYP34A (Section 1.2.4). • Section 7.2.1.5 added to include dose modifications in Part B for subjects on strong CYP3A4 inhibitors. • Added text for concomitant use of strong CYP3A4 inhibitors and required dose reductions and for concomitant use of strong or moderate CYP3A4 inducers (Section 8.2).	Analysis of CC-90009 plasma exposures in subjects who received strong CYP3A4 inhibitors showed elevated exposures when compared to those who were not treated with strong CYP3A4 inhibitors, suggesting a potential DDI and possibility for increased toxicity. Dose reductions are being used as part of the strategy to reduce the risk of sepsis for subjects receiving concomitant strong CYP3A4 inhibitors. Additionally, strong or moderate CYP3A4 inducers may decrease efficacy of CC-90009 and should be avoided.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 9		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.2.4 Safety Monitoring Plan	Added language regarding the Risk-Benefit Assessment.	With the integration of Celgene and BMS' protocol development and risk-benefit assessment processes, the separate Celgene Risk-Benefit Assessment document has been retired. The information on relevant/potential risks and mitigation strategy has been transferred to the updated protocol during a protocol amendment. This change does not impact the Risk-Benefit of the study or compound.

PROTOCOL SUMMARY

Study Title

A Phase 1, Open-label, Dose-Finding Study of CC-90009, a Novel Cereblon E3 Ligase Modulating Drug, in Subjects with Relapsed or Refractory Acute Myeloid Leukemia or Relapsed or Refractory Higher-Risk Myelodysplastic Syndromes

Indication

Relapsed or refractory acute myeloid leukemia (R/R AML)

Relapsed or refractory higher-risk myelodysplastic syndromes (R/R HR-MDS)

Objectives

Primary Objectives:

- To determine the safety and tolerability of CC-90009.
- To define the non-tolerated dose (NTD), the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of CC-90009.

Secondary Objectives:

- To provide information on the preliminary efficacy of CC-90009 in R/R AML and R/R HR-MDS.
- To characterize the pharmacokinetics (PK) of CC-90009 in plasma and urine.

Exploratory objectives and pharmacodynamic (PD) endpoints for the study are outlined in Section 2.

Study Design

Study CC-90009-AML-001 is an open-label, Phase 1, dose escalation and expansion, first-in-human clinical study of CC-90009 in subjects with relapsed or refractory AML (Appendix B) or in subjects with relapsed or refractory higher-risk MDS (Appendix E and G). The dose escalation part (Part A) of the study will evaluate the safety and tolerability of escalating doses of CC-90009, administered intravenously, and determine the MTD of CC-90009. In Part A, two formulations were tested. The expansion part (Part B) will further evaluate the safety and efficacy of CC-90009 administered at or below the MTD in selected expansion cohorts of up to approximately 20 evaluable subjects in each disease indication (R/R AML and R/R HR-MDS) in order to determine the RP2D. One or more dosing regimens may be selected for cohort expansion (at a minimum, one in R/R AML and one in R/R HR-MDS). MDS subjects will only be enrolled during Part B. Parts A and B will consist of 3 periods: Screening, Treatment, and Follow-up. Leukemia response will be determined by the Investigator. Disease assessment will be based on the International Working Group (IWG) Response Criteria in AML (Cheson, 2003; refer to Appendix C). MDS response will be based on the IWG Response Criteria for Myelodysplasia (Cheson, 2006; refer to Appendix F).

Screening Period

The Screening Period starts 28 days prior to first dose of CC-90009. The informed consent document must be signed and dated by the subject and the administering staff prior to the start of any other study procedures. All screening tests and procedures must be completed within the 28 days prior to the first dose of CC-90009. For Part B of the study, subjects will be assigned to either the R/R AML or the R/R HR-MDS cohort based on a central laboratory diagnosis confirmation.

Treatment Period

In the Treatment Period, CC-90009 will be administered intravenously on Days 1-5 of each 28 day cycle for up to 4 cycles in the absence of disease progression (as defined in Section 6.4), relapse, unacceptable toxicity, or subject/physician decision to withdraw. Modified dosing schedules (eg, increasing from 5 consecutive days to up to 7 or 10 consecutive days of dosing or increasing infusion length) may be evaluated in additional cohorts, if necessary, based on toxicity, PK profiles, and PD findings. An additional schedule of CC-90009 administered once daily on Days 1-3 and Days 8-10 of each 28-day cycle will be explored. Those who demonstrate benefit from treatment without unacceptable toxicity (any complete remission [CR], morphologic leukemia-free state [MLFS], partial remission [PR], or stable disease with discussion with Medical Monitor) may continue treatment beyond Cycle 4 until loss of that benefit, unacceptable toxicity, or subject/physician decision to withdraw.

All subjects will be required to start calcium, calcitriol, and vitamin D supplementation at least 3 days prior to Day 1 of each cycle and continue until ≥ 3 days after the last dose of CC-90009 in each cycle (eg, ≥ Day 8 when CC-90009 is administered on Days 1-5, ≥ Day 10 when CC-90009 is administered on Days 1-7, or ≥ Day 13 when CC-90009 is administered on Days 1-10 or Days 1-3/Days 8-10).

In Cycle 1 of Part A, a bone marrow evaluation will be performed on Day 28 (± 3 days). Based on the Day 28 bone marrow evaluation, subjects with hypoplastic bone marrow, without evidence of persistent leukemia, who have Grade ≥ 3 neutropenia will be followed for an additional 2 weeks for safety monitoring in Cycle 1 (total duration of 42 days; refer to Figure 1). An additional bone marrow assessment will be performed at the time of hematologic recovery or Day 42 (± 3 days). Thus, in Part A, the window for evaluation of dose-limiting toxicity (DLT) during Cycle 1 will be up to 42 days (28 or 42 days). In Part B, Cycle 1 will be 28 days in length. Cycles ≥ 2 will be 28 days in length. Subsequent cycles should start ≤ 7 days following the last day of the previous cycle. Permitted treatment delays are described in Section 7.2.12.

Follow-up Period

In the Follow-up Period, all subjects will be followed for 28 days (± 3 days) after the last dose of CC-90009 for safety.

Subjects without documented progression of disease (or relapse) will have efficacy evaluations of complete blood counts and peripheral blood smears performed every subsequent 8 weeks (± 1 week) for the 1st year and every 12 weeks (± 2 weeks) for the 2nd year or until progression of

disease (or relapse), initiation of a new anticancer therapy, withdrawal of consent from the study, death, or the End of Trial, whichever comes first. A bone marrow evaluation will be completed at the end of the 1st year and as clinically indicated during the Follow-up Period.

All subjects will be followed for survival follow-up according to the schedule for the efficacy long-term follow-up for up to 2 years or until death, lost to follow-up, or the End of Trial, whichever occurs first. Survival follow-up may be conducted by record review (including public records) and/or telephone contact with the subject, family, or the subject's treating physician.

Part A-Dose Escalation

During the escalation phase (Part A), a modified accelerated titration design (Simon, 1997) will be used to establish initial toxicity. Cohorts of one or more subjects each will be administered CC-90009 at doses that will increase in 100% increments per cohort until ≥ 2 subjects experience a CC-90009-related Grade ≥ 2 adverse event in the DLT window (may be different cohorts), or ≥ 1 subject experiences a DLT within the DLT window. At that time the current cohort and all subsequent cohorts will be expanded enrolling 3 to 6 subjects. A dose escalation schedule with dose increments not to exceed 50% will concurrently be initiated in order to establish the NTD and MTD (refer to Section 7.2.2). The initial dose will be 0.3 mg. Sample dose escalation schemes are shown in Figure 2. At the study start an initial formulation (Gen 1 CC-90009) will be utilized, and during dose escalation a second formulation (Gen 2b CC-90009) will replace Gen 1 CC-90009. The N,N-Dimethylacetamide (DMA) residual solvent in the Gen 1 CC-90009 formulation must not exceed the permitted daily exposure (PDE) limits set in the ICH *Q3C Impurities: Residual Solvents* in order to proceed with dose escalation cohorts above a daily CC-90009 dose of 2.4 mg. The residual solvent (formic acid) level in the Gen 2b CC-90009 formulation allows daily doses of CC-90009 of up to 20 mg without exceeding its PDE set in the ICH Q3C guidance.

Dose escalation decisions will be made at the discretion of a Safety Review Committee (SRC) that will include Investigators (and/or designated representatives), the Sponsor's study physician, safety physician, and the study manager. Ad hoc attendees may include the study pharmacokineticist, study statistician, and additional study clinical scientists. Other internal and external experts may be consulted by the SRC, as necessary. The Gen 2b CC-90009 formulation was introduced at the fourth dose level (DL4: 2.4 mg D1-5) (in accordance with study dose escalation guidelines) based on SRC recommendation after review of available study data from the initial three dose levels of Gen 1 CC-90009 formulation (0.3 mg D1-5, 0.6 mg D1-5 and 1.2 mg D1-5).

The SRC may decide to evaluate a higher dose cohort, additional subjects within a dose cohort, intermediate dose cohorts, smaller dose increments, alternate dosing schedules (eg, increasing from 5 to up to 7 or 10 consecutive days of CC-90009 administration or longer infusion times), recommend or adjust dose or frequency of premedication requirements, and/or declare an MTD based on their review of available clinical and laboratory safety data, PK profiles, and PD findings. In the event that an alternate dosing schedule is evaluated, the starting dose and schedule will not exceed the dose intensity of a dose cohort that has previously met the criteria for dose escalation.

An additional schedule of CC-90009 administered once daily on Days 1-3 and Days 8-10 of each 28-day schedule may be explored (Figure 3).

After the first dose is administered in any cohort during dose escalation, subjects in each cohort are observed for at least 28 days and up to 42 days (Cycle 1, DLT window) before the next higher, dose cohort can begin. No more than one subject per day will be enrolled in a given dose escalation cohort. A subject evaluable for DLT is defined as one that:

- Has received at least 80% of the total planned Cycle 1 dose (eg, ≥ 4 CC-90009 doses for the Days 1-5 dose schedule to be completed on or before Day 10, ≥ 6 CC-90009 doses for the Days 1-7 dose schedule to be completed on or before Day 10, ≥8 doses by Day 14 for the Days 1-10 schedule, or ≥ 5 doses by Day 14 for the D1-3/D8-10 schedule) of CC-90009 during Cycle 1 without experiencing a DLT,

  Or

- Experienced a DLT after receiving at least one dose (or fraction thereof) of CC-90009.

In the event that an alternate dose schedule (eg, increasing from 5 days to up to 7 or 10 consecutive days of dosing) is evaluated in Part A, the same criteria for determining DLT-evaluable subjects will be applied. Subjects non-evaluable for DLT will be replaced.

A dose level (dose/schedule) will be considered intolerable if > 33% of evaluable subjects in a dose cohort experience DLT during Cycle 1. The MTD will be defined as the last dose below the NTD, at which ≤ 33% of evaluable subjects experienced DLT during Cycle 1. If 2 or more of 6 evaluable subjects experience DLTs in the first dose cohort, a lower dose cohort may be explored at the discretion of the SRC (ie, 0.1 mg CC-90009). An intermediate dose of CC-90009 (one between the NTD and the last dose level before the NTD) may be evaluated to accurately determine the MTD.

Intra-subject dose escalation will not be allowed during the DLT assessment period; however, in Cycles ≥ 2, subjects without evidence of disease progression who are tolerating their assigned dose of CC-90009 may (at the Investigator's discretion) escalate to the highest dose level shown to be adequately tolerated by at least one cohort of subjects in this study (ie, ≤ 33% of evaluable subjects having experienced a DLT at that dose level). If the highest tolerated dose level is Gen 2b CC-90009, a subject currently enrolled on Gen 1 CC-90009 is permitted to switch to the newer formulation.

Part B-Cohort Expansion

Following completion of dose escalation (Part A), one or more dosing regimens may be selected for dose expansion with up to approximately 20 evaluable subjects in each disease indication (R/R AML and R/R HR-MDS) at a specified dose level. Subjects with HR-MDS will be enrolled only during Part B (Figure 4). Note that the 3.6 mg dose of CC-90009 on Days 1-5 schedule with dexamethasone premedication was selected as the Part B dose and schedule in both R/R AML and R/R HR-MDS for the dose expansion part of the study (Part B). Due to a high rate of sepsis (75%) observed in the initial 8 R/R AML subjects enrolled in Part B at dose level 3.6 mg Days 1-5 with dexamethasone premedication, the SRC recommended to close R/R AML and R/R HR-MDS

cohorts receiving CC-90009 at 3.6 mg Days 1-5 for enrollment, and new Part B cohorts will be enrolled under an alternative dosing regimen of 2.4 mg Days 1-7 and 3.0 mg Days 1-7, both to be evaluated in R/R AML and R/R HR-MDS. The selection of the alternative dose and schedule is based primarily on PK and PD analysis and safety and tolerability data. The new Part B cohorts will enroll subjects in parallel. Up to 6 subjects per cohort will be initially enrolled as a safety run-in. The SRC will assess tolerability of the dose and schedule for these initial subjects that completed at least one cycle of study treatment based on the Part A stopping criteria (Section 7.2.8) and recommend further expansion of one or more cohorts. The expanded cohort(s) will be monitored for the excess toxicities including sepsis utilizing the non-binding Bayesian stopping criterion on a continuous basis (Section 9.9.3). Subjects of R/R AML and R/R HR-MDS enrolled in the expansion cohorts may be pooled for analysis of safety, PK, and PD. The SRC will continue to review safety and preliminary efficacy data regularly throughout the study and make recommendations about study continuation and dose modification, as appropriate.

Study Population

Men and women, 18 years or older, with relapsed or refractory AML or relapsed or refractory higher-risk MDS as defined by World Health Organization (WHO) criteria who are not suitable for other established therapies, will be enrolled in the study.

In Part A, only R/R AML subjects will be enrolled. In Part B, one of the initial cohorts will include R/R AML subjects, including subjects who relapse after allogeneic HSCT, who are in second or later relapse, who are refractory to initial induction or re-induction treatment, who are refractory to or relapsed after receiving hypomethylating agents (HMA failure defined as primary progression or lack of clinical benefit after a minimum of 6 cycles or unable to tolerate HMA due to toxicity), or who relapse within 1 year of initial treatment (excluding those with favorable-risk status; see Appendix H).

In Part B, one of the initial cohorts of R/R HR-MDS subjects will be treated including subjects who score > 3.5 points in the Revised International Prognostic Scoring System (IPSS-R) [eg, IPSS-R intermediate risk (in combination with more than 10% bone marrow blasts or poor or very poor IPSS-R cytogenetic risk), IPSS-R high and IPSS-R very high risk] and are not suitable for other established therapies (eg, transplant or hypomethylating agent) (Appendix G).

Length of Study

Enrollment is expected to take approximately 62 to 68 months to complete (50 months for dose escalation, and approximately 12 to 18 months for expansion). Completion of active treatment and post-treatment follow-up is expected to take an additional 6 to 24 months. The entire study is expected to last up to approximately 6 to 8 years.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary, and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

Study Treatments

Celgene Corporation (Celgene) will supply the investigational product, CC-90009 for IV injection, labeled appropriately for investigational use as per the regulations of the relevant country health authority. Study drug will be administered as outlined in the **Treatment Period** section above.

Study treatment may be discontinued if there is evidence of clinically significant disease progression (or relapse), unacceptable toxicity or subject/physician decision to withdraw. Subjects may continue to receive study drugs beyond disease progression at the discretion of the Investigator in consultation with the Celgene Medical Monitor.

Overview of Key Efficacy Assessments

The primary efficacy variable is response rate.

All treated subjects will be included in the efficacy analyses. Leukemia response will be determined by the Investigator. Disease assessment will be based on the International Working Group (IWG) Response Criteria in AML (Cheson, 2003; refer to Appendix C). Overall response will be determined using the IWG Response Criteria for Myelodysplasia for the HR-MDS cohort (Cheson, 2006; Appendix F).

A descriptive analysis of evidence of antileukemic activity will be provided based on clinical, laboratory, molecular, and cytogenetic assessments by Investigator, which includes assessment of bone marrow blast percentage, bone marrow cytogenetics, molecular genetic studies to evaluate molecular responses, bone marrow flow cytometry, platelet count, and absolute neutrophil count.

AML and MDS response criteria will be summarized by best overall response categories: complete remission rate (CRR), and objective response rate (ORR). For AML, the ORR includes all responses of complete remission (CR) (ie, morphologic CR, cytogenetic CR, molecular CR, morphologic CR with incomplete blood recovery, and morphologic CR with partial hematologic recovery), morphologic leukemia-free state (MLFS), and partial remission. For MDS, the ORR includes all responses (CR, marrow complete remission [mCR], and PR).

The efficacy variable of focus will be ORR and CRR. Other measures of clinical activity including overall survival (OS), relapse-free survival (RFS), progression-free survival (PFS), event-free survival (EFS), duration of remission, duration of response, time to transformation (TTT) to AML (HR-MDS subjects only) and time to remission/response (TTR) will be summarized.

Overview of Key Safety Assessments

The safety variables for this study include adverse events, safety clinical laboratory variables, 12-lead electrocardiograms, Eastern Cooperative Oncology Group Performance Status, left ventricular ejection fraction assessments, physical examinations, vital signs, exposure to study treatment, assessment of concomitant medications, and pregnancy testing for females of childbearing potential.

Overview of Key Pharmacokinetic Assessments

Key plasma PK parameters determined for CC-90009 will include maximum observed concentration (C_{max}), area under the plasma concentration-time curve from time 0 to 24 hours

postdose (AUC_{24}), terminal-phase elimination half-life ($t_{1/2}$), total plasma clearance (CL), time to peak (maximum) plasma concentration (t_{max}), volume of distribution at the steady state (Vss), percent dose excreted in urine as unchanged (F_e) and renal clearance (CL_R). Selected PK parameters (eg, C_{max}, AUC_{24}, $t_{1/2}$) will be estimated for R- and S-enantiomers of CC-90009 as appropriate. Key plasma and urine PK parameters as described above will also be estimated for hydroxypropyl-β-cyclodextrin (HPBCD).

Statistical Methods

Statistical analyses will be performed by dose level (Part A) and cohort (Part B) as needed or applicable. All analyses will be descriptive in nature.

All summaries of safety data will be conducted using subjects receiving any CC-90009 (the Treated Population).

The efficacy variables of primary interest are the ORR and CRR. Other preliminary efficacy variables including OS, RFS, PFS, event-free survival, duration of remission, duration of response, and time to remission/response will be summarized. Efficacy analysis will be repeated for the Treated Population and Efficacy Evaluable Population (received a baseline leukemia assessment evaluation, at least one cycle of study treatment or at least 80% of scheduled doses in Cycle 1, and one on-study leukemia assessment evaluation), with the result using the Treated Population considered primary.

All biomarker-related data presentations will be based on treated subjects with at least one biomarker assessment, unless specified otherwise. Descriptive statistics will be presented for baseline and change from baseline of continuous biomarker endpoints, by dosing regimens and/or disease subsets, and overall.

Exploration of PK, PD, safety and activity relationships will be assessed.

During the Part A dose escalation, 72 subjects were enrolled. During the Part B dose expansion, at least 13 efficacy evaluable subjects with R/R AML will be accrued. If the response rate is 30% or more, the probability of seeing no response in the first 13 R/R AML subjects will be less than 1% (Gehan, 1961). If no responder is observed out of 13 R/R AML subjects, the enrollment for this cohort will stop for futility. Otherwise, the cohort will be expanded to up to approximately 20 evaluable subjects each for R/R AML and R/R HR-MDS of a selected dosing regimen if a responder is observed.

During the Part B dose expansion, a non-binding Bayesian method will be utilized to monitor excess toxicities defined as the occurrence of adverse events (AEs) during any cycle that would fulfill the DLT criteria specified in Part A or treatment related AEs leading to dose reduction or discontinuation or the occurrence of sepsis (Section 9.9.3). The enrollment in the corresponding expansion cohort may pause to ensure the posterior probability of excess toxicity rate exceeding 25% is not more than 70%. After a minimum of 8 subjects have enrolled and taken at least one cycle of study treatment for a cohort, the posterior distributions of excess toxicity will be calculated on a continuous basis for every subject enrolled (Table 15). If the stopping rule is triggered, the

SRC will conduct a comprehensive review of available safety, PK, PD, and efficacy data to make continuation decisions.

The study will be conducted in compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/Good Clinical Practice and applicable regulatory requirements.

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1 INTRODUCTION

CC-90009 is a small molecule being developed for the treatment of acute myeloid leukemia (AML) and higher-risk myelodysplastic syndromes (MDS) and is a member of a class of agents identified as cereblon (CRBN) E3 ligase modulating drugs. CC-90009 was strongly antiproliferative in the majority of AML cell lines tested (10 out of 11) as well as in primary AML patient samples and exerted its effects through rapid induction of apoptosis. CC-90009 also reduced tumor cell numbers in bone marrow in the HL-60 intravenous (IV) xenograft model of AML. CC-90009 had potent antiproliferative and cytotoxic activity against both an MDS cell line and HR-MDS patient derived bone marrow cells assayed ex vivo. The potent antiproliferative activity of CC-90009 is cereblon-dependent and entails induction of an unfolded protein response (UPR). Cereblon is the substrate receptor component of the cullin ring ligase (CRL)4/cereblon/E3-ubiquitin ligase complex that recruits specific proteins to the complex for ubiquitination and subsequent proteasomal degradation.

1.1 Disease Background

1.1.1 Acute Myeloid Leukemia

Acute myeloid leukemia is the most commonly reported type of acute leukemia in adults in the United States (US). Based on the American Cancer Society's estimates, approximately 20,830 people will be diagnosed with AML in 2015 in the US and 10,460 patients will die from the disease (American Cancer Society, 2015). The median age at diagnosis is approximately 67 years.

Acute myeloid leukemia can arise *de novo*, be secondary to previous cytotoxic chemotherapy, or arise through transformation of existing myelodysplasia. Therapy-related AML arising from exposure to environmental toxins, cytotoxic drugs, or radiation currently accounts for about 5% to 10% of all cases of AML (Leone, 1999). It is estimated that 35% to 40% of patients with myelodysplastic syndromes will go on to develop AML, with the disease often refractory to current therapy (Silverman, 2000). Preexisting myelodysplastic or myeloproliferative disorders are common in older patients with AML, occurring in 24% to 40% of cases (Gajewski, 1989). Patients with secondary AML due to prior hematologic disease have a lesser response to therapy than those with *de novo* disease. In the series from the Southwest Oncology Group, for example, the complete remission (CR) rates were 24% and 52%, respectively (Leith, 1997, Gajewski, 1989.

The usual treatment of AML is divided into two phases: induction of remission and consolidation therapy. For more than 30 years, the combination of cytarabine and an anthracycline has been the mainstay of treatments to induce remission (Lowenberg, 1999; Tallman, 2005). The remission induction therapy in leukemia is designed to produce the rapid restoration of normal bone marrow function. A common induction regimen consists of cytarabine, 100 mg/m^2/day for 7 days combined with daunorubicin 45-60 mg/m^2/day for 3 days, often referred to as the "7+3 protocol." With the combination of cytarabine and daunorubicin or their analogues, a CR, conventionally defined morphologically by the presence of < 5% blasts in the bone marrow together with the recovery of peripheral-blood absolute neutrophil and platelet counts, can be achieved in up to 70% to 80% of adults with *de novo* AML who are < 60 years of age (Lowenberg, 1999; Tallman, 2005).

If CR is achieved, there are 3 basic treatment choices for post-remission therapy: additional chemotherapy, stem cell transplantation from a donor (allogeneic stem cell transplantation), or stem cell transplantation using the patient's own stem cells (autologous stem cell transplantation). For post-remission chemotherapy, the same chemotherapy regimen used for remission induction or a higher dose regimen of cytarabine is often repeated for one or more cycles, referred to as consolidation chemotherapy. When several courses of consolidation are given, survival rates at 2-3 years are 35% to 50% for young to middle-age adults who have achieved CR (Milligan, 2006). However, consolidation or post-remission chemotherapy for elderly patients with AML has not been proven beneficial.

Importantly, AML is mostly a disease of older individuals with a median age at diagnosis of approximately 67 years. Older patients with AML have significant comorbidities, more unfavorable cytogenetic abnormalities, a poorer performance status, and a higher incidence of AML arising from MDS. Moreover, older patients are more likely to have increased multidrug resistance to chemotherapy, inability to tolerate intensive chemotherapy, which may be responsible in large part for the poor outcomes observed in older-aged subgroups. In elderly AML patients, defined as older than 60 years, conventional cytotoxic intensive chemotherapy has been associated with CR rates of approximately 45%, considerably lower than in younger patients (Jabbour, 2006). Unfortunately, the duration of remission is shorter, the early treatment-related mortality is high, approximately 30% to 50% (Jabbour, 2006), which in part explains a median survival time between 7 to 12 months (Dombret, 2008; Burnett, 2007).

Given the poor overall outcome and high treatment-related mortality in older AML patients, some physicians do not pursue aggressive induction therapy, opting for less aggressive therapies. Treatment options are few for patients who choose not to receive intensive chemotherapy or are considered ineligible (unfit) to receive intensive chemotherapy by their physician. Patients considered ineligible for intensive chemotherapy are generally patients older than 75 years or those 60 to 75 years old with significant comorbidities, poor performance status, or with complex cytogenetic abnormalities (NCCN 2017a; Milligan, 2006). Treatment options for these patients include low-intensity therapies such as low-dose cytarabine or supportive care only. In a Medical Research Council (MRC) AML14 study, low-dose cytarabine (20 mg twice daily for 10 days) was compared to best supportive care including hydroxyurea in patients with AML who were greater than 65 years of age and considered ineligible for intensive chemotherapy by the Investigator (Burnett, 2007). No specific criteria were used to determine the patient's eligibility for chemotherapy other than those patients at least 70 years old who had to have a documented comorbidity that precluded chemotherapy. The low-dose cytarabine group demonstrated a higher CRR (18%) compared to hydroxyurea (1%). Overall survival was also significantly better in the low-dose cytarabine group, but only approximately 50% of the patients were alive at 4 months and 25% were alive at 1 year (Burnett, 2007). In a retrospective analysis of 36 AML studies with a median age of 70 years, patients receiving low-intensity therapies or best supportive care had a median overall survival of approximately 3 months and 2 months, respectively (Deschler, 2006). Despite a survival benefit with the use of less intensive chemotherapy such as low-dose cytarabine in this elderly AML population, the outcome remains unsatisfactory.

1.1.2 Higher-Risk Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) is an umbrella term for a heterogeneous collection of hematopoietic stem cell disorders primarily affecting older adults. It is estimated that between 2 and 4 cases per 100,000 persons per year are diagnosed with MDS. The elderly are particularly vulnerable with annual incidence rates between 15 and 50 cases per 100,000 persons per year (Steensma, 2003). The prognosis depends on the individual's risk factors, with a median survival ranging from 5.3 years in low-risk patients to 1.6 and 0.8 years in high- or very high-risk patients (Greenberg, 2012).

Myelodysplastic syndromes is typically characterized by ineffective hematopoiesis in the bone marrow (BM) and peripheral blood cytopenias that manifest clinically as anemia, neutropenia, and/or thrombocytopenia of variable frequency and severity. Anemia is the most frequent laboratory finding and it often progresses to red blood cell (RBC) transfusion dependence. Other less common presenting clinical features related to the cytopenias are an increased risk of infection and/or hemorrhage and a propensity to progress to acute myeloid leukemia (AML) (Catenacci, 2005).

For certain subtypes of MDS, excess blast cells are present (Bennett, 1982). Progress in understanding the pathobiology of MDS has evolved rapidly, as have an increasing number of myeloablative and supportive care strategies. The mainstay of therapy has been supportive care, which includes the use of red cell or platelet transfusions, treatment of infections, and the use of epoetin alfa or myeloid growth factors when needed (NCCN, 2017b; Silverman, 2000; Lübbert, 2000). Vidaza (azacitidine) has been shown to increase overall survival in patients with higher-risk myelodysplastic syndromes relative to conventional care but is not curative (Fenaux, 2009). Bone marrow transplantation has been effective both in patients under the age of 50 and in those older than 50 who are in good health. However, this approach has limited value, since most patients with MDS are older than 65 years of age and have significant comorbidities (NCCN, 2017b; Silverman, 2000).

Major MDS prognostic risk scoring systems and predictors have been developed over the years. Changes in risk of mortality and of leukemic transformation over time were recently compared in a multicenter retrospective study which included 7212 primary untreated MDS patients (Pfeilstöcker, 2016). The analysis of hazards regarding mortality and AML transformation risk suggested a division into lower- and higher-risk MDS based on the IPSS-R (Greenberg, 2012) cutoff of 3.5 points. For this study, higher-risk MDS will be defined as patients with > 3.5 points in the IPSS-R system (Greenberg, 2012, Pfeilstöcker, 2016). This includes all patients in the High (> 4.5 – 6) and Very High (> 6) IPSS-R risk groups as well as a sub-population of those in the Intermediate (> 3-4.5) category. High and Very High risk groups had a median survival of 1.6 and 0.8 years respectively, and the subpopulations with poor and very poor cytogenetics with median survival of 1.5 and 0.7 years respectively or a blast count > 10% (survival 1.3 years) (Greenberg, 2012). Relapsed or refractory higher-risk MDS patients are a high-unmet need population for which there is no standard of care and novel therapies are needed.

1.2 Compound Background

Please refer to the CC-90009 Investigator's Brochure (IB, CC-90009 IB) for detailed information concerning the available pharmacology, toxicology, and drug metabolism of the investigational product (IP).

1.2.1 Nonclinical Pharmacology

1.2.1.1 Mechanism of Action

CC-90009 is a potent antitumor agent in vitro demonstrating strong antiproliferative activity against AML cell lines. CC-90009 inhibited cell growth in 10 of the 11 cell lines in a representative panel of AML cell lines that included a range of common oncogenic AML mutations (IC_{50} = 3 to 75 nM). The antiproliferative activity of CC-90009 is achieved through rapid induction of apoptosis. The mechanism of action of CC-90009 entails induction of an UPR. The potent antiproliferative activity of CC-90009 is CBRN-dependent, as CC-90009 did not inhibit growth in CBRN-deficient constructs of sensitive AML cell lines. Cereblon is the substrate receptor component of the CRL4/CBRN/E3–ubiquitin ligase complex that recruits specific proteins to the complex for ubiquitination and subsequent proteasomal degradation. CC-90009-induced CBRN substrates and markers of UPR will be used as pharmacodynamics (PD) mechanism markers.

1.2.1.2 In Vitro Pharmacology

CC-90009 had potent anti-proliferative and cytotoxic activity against both an MDS cell line (sub nM IC_{50}) and HR-MDS patient derived bone marrow cells assayed in ex vivo. CC-90009 strongly inhibits both proliferation and self-renewal activity of bone marrow cells derived from HR-MDS patients, compared to age matched normal donor controls, suggesting a therapeutic index may be achieved in HR-MDS.

Effect on Hematopoiesis in Normal Donor Bone Marrow Samples

The effect of CC-90009 on hematopoietic progenitors was evaluated using colony forming assays in bone marrow cluster of differentiation (CD)34+ cells derived from four individual healthy donors. Inhibition of granulo-monocytic progenitors (half-maximal inhibitory concentration [IC_{50}] = 82 to 135 nM) and erythroid progenitors (IC_{50} = 32 to 131 nM) derived from normal bone marrow was observed. At 8 hours exposure, the effect on hematopoietic progenitors was reduced in intensity relative to continuous exposure to CC-90009 for 14 days and, at 2 or 4 hours exposure, the inhibitory effect of CC-90009 was absent. The data suggest that the impairment of growth of hematopoietic progenitors by CC-90009 may be effectively managed if dose and time of exposure are reduced.

Effects of CC-90009 on neutrophil maturation in normal bone marrow samples were evaluated by two-dimensional cultivation of progenitors followed by assessment of cell differentiation and apoptosis. There was no reduction in viability in cultures exposed to 0.03 to 30 nM CC-90009 for 8 hours or to ≤ 3 nM CC-90009 for 24 or 72 hours. However, there was reduction in viability in cells exposed to 30 nM CC-90009 for 24 or 72 hours. Removal of CC-90009 after 72 hours and subsequent incubation for the remainder of the 14-day differentiation period led to improvement in viability. Surviving cells were able to proliferate and fully mature to normal neutrophils.

Antitumor Activity in AML versus Normal Bone Marrow Samples

The antitumor activity of CC-90009 in 4 AML patient bone marrow samples was explored in a semi-solid culture system and compared with the results for normal bone marrow samples. CC-90009 did not demonstrate greater activity against progenitors in bone marrow of AML patients versus normal donors. The antiproliferative activity of CC-90009 against hematopoietic progenitors in AML patient bone marrow samples (IC_{50} of 7.8 to 94 nM) was broadly similar to that in normal bone marrow samples (IC_{50} = 8.6 to 10.7 nM).

The antitumor activity of CC-90009 in bone marrow aspirates derived from 30 AML patients during patient diagnosis was evaluated in a test system ex vivo that did not separate the samples into constituent cells and thereby retained the microenvironment of bone. CC-90009 demonstrated potent activity in 26 of the 30 AML patient samples (average EC_{50} = 21 nM [range 2 to 160 nM] across all 3 time points in the 26 sensitive AML patient samples). Leukemic cell killing was rapid and efficient in the sensitive patient samples in that, on average, > 82% of leukemic cells were depleted by 24 hours, > 92% by 48 hours, and > 98% by 96 hours. Furthermore, in patient samples where sufficient normal lymphocytes could be counted, CC-90009 exhibited only modest antiproliferative activity against the normal cells (maximum possible effect [Emax] averaged 46% to 76% from 24 to 96 hours). CC-90009 displayed a differential potency between leukemic and normal hematopoietic cells of 2- to 5-fold across the three time points.

The results indicate that addition of CC-90009 to ex vivo cultures of healthy donor bone marrows resulted in decreased/delayed formation of granulo-monocytic and erythroid colonies by inducing cell growth delay or arrest without reducing survival of the hematopoietic stem cells or hematopoietic progenitors for 8 hours. The findings suggest the possibility of devising dosing strategies for elimination of AML cells that spare normal hematopoietic stem/progenitor cells and permit neutropenia to be reversed.

Therapeutic Window

The findings of several different investigations point to the selectivity of CC-90009 for antiproliferative activity in AML cells versus normal cells. CC-90009 demonstrated greater antiproliferative activity in vitro in sensitive AML cell lines than in activated, rapidly proliferating peripheral blood mononuclear cells (PBMCs) or in THLE-2 cells, a non-tumorigenic immortalized human hepatocyte cell line (IC_{50} = 5.5 μM). The induction of apoptosis by CC-90009 was 3- to 7-fold greater in a sensitive AML cell line than in PBMCs. CC-90009 demonstrated potent activity that entailed rapid and efficient leukemic cell killing in 26 of 30 AML patient bone marrow samples ex vivo while exhibiting only modest antiproliferative activity against the normal cells in the same samples. Overall, the results suggest the potential of a therapeutic window for CC-90009 in AML patients.

CC-90009 incubation of AML cell lines in vitro and AML patient-derived bone marrow mononuclear cells ex vivo resulted in significant increases in IL-1 proteins that could be blocked by inhibiting apoptosis. This suggested that CC-90009-induced apoptosis may lead to release of IL-1 and result in systemic cytokine exposure and hypotension in patients. Dexamethasone (but

not indomethacin or celecoxib) significantly reduced IL-1b levels induced by CC-90009 in AML cell lines.

1.2.1.3 In Vivo Pharmacology

CC-90009 antitumor activity was assessed in the HL-60 xenograft model of AML. Although an initial study did not result in evidence of improved survival in CC-90009-treated animals, a second study in which bone marrow was examined did reveal a substantial reduction in numbers of tumor cells in bone marrow of CC-90009-treated animals with two dosing schedules [5 mg/kg twice a day (BID) x 5 days or 2.5 mg/kg BID x 10 days]. These data indicate that the two dosing schedules can achieve approximately equivalent efficacy.

1.2.1.4 In Vivo Pharmacokinetics

In animal models, CC-90009 demonstrated low clearance and extensive distribution. Minimal (rat) or no (monkey) sex differences in pharmacokinetics (PK) or toxicokinetics (TK) were noted across studies. Overall, CC-90009 showed acceptable PK properties in single-dose and repeat-dose TK studies.

CC-90009 was metabolized primarily via non-enzymatic (hydrolysis) and enzymatic pathways. Although there were quantitative interspecies differences in the formation of metabolites, qualitatively all metabolites formed in human hepatocytes were also formed in rat and/or monkey hepatocytes, the species used for preclinical safety testing.

CC-90009 (up to 2.5 μM) did not cause inhibition and induction of cytochrome P450 (CYP) enzymes in in vitro studies except for moderate inhibition of CYP2C9 (41% at 2.5 μM) and CYP2C19 (IC50 = 1.53 μM). Even though CC-90009 is not anticipated to cause drug interactions when administered with CYP2C9 and CYP2C19 substrates at clinically relevant concentrations, caution should be used with narrow therapeutic index substrates such as warfarin, consistent with general clinical practice.

In humans, using the PK parameters of CC-90009 in monkeys and single species allometric scaling, CC-90009 is predicted to have low clearance (18.9 L/hr, up to approximately one-fourth liver blood flow) and high volume of distribution (1.44 L/kg, up to approximately 3-fold total body water volume).

1.2.2 Nonclinical Toxicology

The toxicity of CC-90009 has been characterized in a core battery of repeat-dose toxicity studies in rats and monkeys using intravenous bolus injection as the route of administration and in the in vitro genotoxicity studies.

In the CC-90009 pivotal 28-day (with a 28-day recovery period) intravenous rat toxicity study, there were no CC-90009-related effects noted up to the highest dose of 5 mg/kg/day, which was the maximum feasible dose that could be given to rats based on the tolerability of the vehicle. Based on the absence of CC-90009-related findings, the severely toxic dose in 10% (STD10) of rats for this study was considered to be greater than 5.0 mg/kg/day and the no observable effect level (NOEL) was determined to be 5.0 mg/kg/day, the top dose administered, corresponding to a combined-sex mean plasma concentration at 5 minutes postdose (C_{5min}) of 5420 ng/mL and the

combined-sex mean area under the plasma concentration-time curve calculated to the last observable concentration at time t (AUC_t) of 8050 ng•h/mL on Day 28. These C_{5min} and AUC_t were 32- and 22-fold greater than those obtained at the highest dose of 0.3 mg/kg/day tested in the pivotal 28-day monkey study.

In the CC-90009 28-day (with a 28-day recovery period) intravenous monkey toxicity study, adverse effects on clinical condition (including inappetence, decreased activity, tremors, and unsteady movement) were observed in males and females administered 0.1 mg/kg/day for 28 days and in females administered 0.3 mg/kg/day on Days 1 to 5 and 15 to 19. Decreased sternal bone marrow cellularity was observed in males and females dosed at ≥ 0.1 mg/kg/day and was reflected in decreases in reticulocyte counts. The severity of bone marrow hypocellularity ranged from minimal to marked at 0.1 mg/kg/day for 28 days and from slight to moderate at 0.3 mg/kg/day for a total of 10 days. Based on the marked severity of bone marrow hypocellularity in one male at 0.1 mg/kg/day and a lack of complete recovery in one female at 0.3 mg/kg/day, these doses were considered severely toxic doses to the monkeys. Therefore, the no observed adverse effect level (NOAEL) and the highest non-severely toxic dose (HNSTD) was 0.03 mg/kg/day, corresponding to a mean C_{5min} of 16.7 ng/mL and a mean AUC_t of 30.6 ng·hr/mL for combined sexes on Day 28.

Decreased total calcium (Ca) levels were noted in the pivotal 28-day monkey study when animals were treated at 0.1 mg/kg/day for 28 days or at 0.3 mg/kg/day on Days 1 to 5 and Days 15 to 19. When compared to pretest values, mean total Ca levels were 11% and 17% lower on Day 27 in males and females treated at 0.1 mg/kg/day, respectively. In males and females treated at 0.3 mg/kg/day, mean values were 19% and 15% lower, respectively, on Day 18 (4^{th} day of the second 5-day cycle). These decreases were not considered adverse, and were, at least in part, due to decreases in total protein, albumin, and globulin levels observed in these dosage groups. However, in an earlier exploratory study, an approximately 50% decrease in total serum Ca level was observed when cynomolgus monkeys were dosed at 0.3 mg/kg/day for 7 days. In addition, more severe clinical signs of ataxia, hunched posture, tremors, tonic convulsions, dilated pupil(s), lateral recumbency, clenched fists, and inappetence were observed in these animals. In order to investigate the relationship of these signs to a reduction in serum calcium, another monkey study was conducted with animals dosed at 0.3 mg/kg/day for up to 14 days, with or without calcium and vitamin D supplementation, with a 14-day recovery period. The purposes of this study were to measure ionized Ca level, to investigate effect of calcium and vitamin D supplementation on serum Ca level and clinical condition of monkeys during CC-90009 treatment, and to assess reversibility of clinical effects when dosing was terminated.

The data from this study demonstrate a strong correlation between clinical signs and calcium levels. All CC-90009 treated animals without calcium and vitamin D supplementation tolerated 5 daily doses of 0.3 mg/kg with the exception of one male who received only 4 doses and needed IV calcium supplementation to recover. A drop in calcium level was first observed on Day 3 of dosing. During the recovery period for animals that received 5 days of treatment, the reversibility of calcium level and clinical signs was observed within 2 days after cessation of dosing. These animals did not need calcium supplementation for their recovery.

In the group of animals with calcium and vitamin D supplementation (started prior to CC-90009 dosing), improved tolerability with significantly prolonged duration of dosing (range = 6 to 13 days with mean duration of 10 days; 4/10 animals received 13 doses) were observed. In these animals, the drop in calcium level was also first observed on Day 3, but the decreases were mild. Clinical signs were similar but with a later onset and decreased severity.

These data from multiple monkey studies showed that the decreases in serum Ca level were dose- and duration-dependent, and the magnitude of reduction became adverse only when a dose of 0.3 mg/kg/day was given longer than 5 days without supplementation. At the HNSTD and NOAEL of 0.03 mg/kg/day in the pivotal monkey study, there was no change in total serum Ca at the end of 28 days of continuous daily treatment. Furthermore, in all 3 dose groups in the 28-day Good Laboratory Practice (GLP) toxicity study, animals did not exhibit severe clinical signs as those seen in the second GLP monkey study when a dose of 0.3 mg/kg/day was administered for longer than 5 days. Therefore, data from the investigative study, though provided more information, did not change the overall conclusions of the 28-day monkey study. All of these data have been taken into consideration for clinical trial design and management of potential hypocalcemic effect of CC-90009 in humans.

CC-90009 was not mutagenic when tested in the bacterial reverse mutation assay. In the in vitro chromosomal aberrations assay using the Chinese Hamster Ovary (CHO) cells, CC-90009 was positive for the induction of structural and negative for the induction of numerical chromosome aberrations under the non-activated treatment condition. CC-90009 was negative for the induction of structural and numerical chromosome aberrations under the S9-activated treatment condition.

Please refer to the most current version of CC-90009 IB for the latest, detailed clinical information concerning pharmacology, toxicology, drug metabolism, patient outcomes, and the adverse event (AE) profile of CC-90009.

1.2.3 Prior Clinical Experience with CC-90009

A summary of clinical experience with CC-90009 as of 17 Feb 2021 is provided in the CC-90009 Investigator's Brochure (IB), Edition 7.0 (CC-90009 IB, 2021), based on two ongoing studies, CC-90009-AML-001 (a first-in-human study of CC-90009 monotherapy in subjects with R/R AML or R/R HR-MDS) and CC-90009-AML-002 (a Phase 1b study of CC-90009 in combination with anti-leukemia agents in subjects with AML). A planned study of CC-90009-CP-001 is a clinical pharmacology study in healthy male subjects. Most extensive clinical information comes from the CC-90009-AML-001 study. Please refer to the most current version of CC-90009 IB for the latest, detailed clinical information concerning pharmacology, toxicology, drug metabolism, patient outcomes, and the adverse event (AE) profile of CC-90009.

1.2.3.1 Study CC-90009-AML-001

Enrollment of subjects in Part A Dose Escalation of the study has been completed and a total of 72 subjects were treated. (One subject, in the 3.6 mg with dexamethasone premedication cohort, was reenrolled under a new subject number after discontinuing from study and subsequently relapsing after 8 months of complete remission. The subject's two subject numbers were consolidated, and they were counted only once.) All treated subjects had R/R AML. To date, 4

dosing schedules of CC-90009 have been explored; once daily dosing on Days 1-5 of a 28-day cycle (0.3 mg to 4.5 mg), Days 1-7 of a 28-day cycle (3.6 mg), Days 1-10 of a 28-day cycle (3.0 mg), and Days 1-3 and 8-10 of a 28-day schedule (3.0 and 3.6 mg). Dose levels of 3.6 mg and above and the 3.0 mg dose level on the Days 1-10 schedule included premedication with dexamethasone for subjects enrolling starting with Protocol Amendment 5. As of 01 Apr 2021, enrollment in Part A of the study has been completed. After a review of Part A data, the SRC recommended that CC-90009 be dosed at 3.6 mg on Days 1–5 with dexamethasone premedication in Part B Dose Expansion in both R/R AML and R/R HR-MDS. After review of initial data from Part B Dose Expansion with an observation of a higher rate of sepsis in the Part B R/R AML cohort as compared to R/R AML cohorts in Part A, the SRC recommended to close R/R AML and R/R HR-MDS cohorts receiving CC-90009 at 3.6 mg Days 1–5 for enrollment, and two new dose levels (2.4 mg and 3.0 mg on Days 1-7) were recommended to be expanded as part of a dose optimization and sepsis mitigation strategy.

As of the 13 Aug 2021 cutoff date, preliminary data are available for 80 subjects with R/R AML and 2 subjects with R/R HR-MDS. Of the 82 subjects treated with CC-90009, 79 (96.3%) had discontinued from treatment and out of these, 76 (92.7%) had discontinued from the study. The most common reason for treatment discontinuation was progressive disease in 24 (29.3%) subjects. The most common reason for study discontinuation was death in 67 (81.7%) subjects.

The median age of all enrolled subjects was 65 years (range: 19 to 81) and most subjects (67.1%) were male. At baseline, most subjects had an ECOG score of 0 (28.0%) or 1 (62.2%). Eight (9.8%) subjects had a baseline ECOG score of 2. Of those with AML, all subjects had previously been treated for AML; most had received 1 or 2 prior therapies (25.6% and 23.2% of subjects, respectively). Forty-eight (58.5%) subjects had 1 previous complete remission or partial remission with prior treatment, 59 (72.0%) were refractory to their last therapy, and 33 (40.2%) have experienced only treatment failure. Of the subjects with AML, the median time from initial AML diagnosis to the date of first dose was 0.89 years (0.0-11.6 years). Twenty-seven (32.9%) subjects had secondary AML, and 25 (30.5%) subjects had AML secondary to prior MDS.

In Part A, responses occurred at exposures achieved with a dose of CC-90009 ≥ 3 mg on schedules with 5 or more consecutive dosing days. Objective responses were seen in subjects treated at doses of 3.0 and 3.6 mg. One (33.3%) subject in Dose Level 5 (3.6 mg on Days 1 to 5) had a response of MLFS, 1 (6.7%) subject in Dose Level 6 (3.0 mg on Days 1 to 5) had a response of CRi, 2 (25.0%) subjects in Dose Level 9 (3.6 mg with dexamethasone premedication on Days 1 to 5) had a response (CR in 1 subject and CRi in the second subject), 4 (57.1%) subjects in Dose Level 11 (3.6 mg on Days 1 to 7) had a response (CR in 2 subjects and MLFS in 2 subjects), and 3 (33.3%) subjects in Dose Level 12 (3.0 mg on Days 1 to 10) had a response (CRi in 2 subjects and MLFS in 1 subject). In Part B at 3.6 mg with dexamethasone premedication on Days 1 to 5, 2 (25.0%) subjects in the R/R AML cohort had a response (CRi in 1 subject and MLFS in the second subject).

All 82 (100.0%) subjects had at least 1 treatment-emergent adverse event (TEAE) and 77 (93.9%) subjects had at least 1 TEAE suspected by the investigator to be related to CC-90009. Seventy-three (89.0%) subjects had at least 1 Grade 3/4 TEAE, 70 (85.4%) subjects had at least 1 treatment-

emergent serious adverse event (TESAE), 31 (37.8%) subjects had at least 1 TEAE leading to CC-90009 dose interruption, 3 (4.2%) subjects had at least 1 TEAE leading to CC-90009 dose reduction, 7 (8.5%) subjects had at least 1 TEAE leading to the permanent discontinuation of CC-90009, and 27 (32.9%) subjects had at least 1 TEAE leading to death.

The TEAEs occurring in ≥ 20% of subjects overall were hypocalcemia (64 subjects; 78.0%), nausea (49 subjects; 59.8%), diarrhea (49 subjects, 59.8%), hypotension (46 subjects; 56.1%), vomiting (31 subjects; 37.8%), hypokalemia (29 subjects; 35.4%), febrile neutropenia (23 subjects; 28.0%), hypomagnesemia (24 subjects; 29.3%), fatigue (21 subjects; 25.6%), ALT increased and AST increased (19 subjects each; 23.2%), hypophosphatemia (21 subjects; 25.6%), acute kidney injury (17 subjects, 20.7%), and decreased appetite (19 subjects; 23.2%).

Seventy-seven (93.9%) subjects had at least 1 TEAE suspected by the investigator to be related to CC-90009. Treatment-emergent AEs suspected by the investigator to be related to CC-90009 that occurred in ≥ 10% of subjects overall were hypocalcemia (60 subjects; 73.2%); hypotension (38 subjects; 46.3%); nausea (36 subjects; 43.9%); diarrhea (30 subjects; 36.6%); vomiting (23 subjects; 28.0%); ALT increased (15 subjects; 18.3%); AST increased, fatigue, decreased appetite, and hypokalemia (14 subjects; 17.1% each); hyperphosphatemia (13 subjects, 15.9%); hypomagnesemia (11 subjects, 13.4%); dizziness, hypophosphatemia, and blood creatinine increased (10 subjects, 12.2% each); and acute kidney injury (9 subjects; 11.0%).

Overall, 27 (32.9%) subjects had at least 1 TEAE leading to death. These included acute myeloid leukemia in 7 (8.5%) subjects, sepsis in 6 (7.3%) subjects, and pneumonia and septic shock in 2 (2.4%) subjects each. All other TEAEs leading to death occurred in 1 subject each: bacterial sepsis, cardiac arrest, general physical health deterioration, hyperglycemic hyperosmolar nonketotic syndrome, Klebsiella sepsis, multiple organ dysfunction syndrome, pneumonia pseudomonal, pulseless electrical activity, sepsis syndrome and Stenotrophomonas sepsis. Eight (9.8%) subjects had at least 1 TEAE leading to death that was suspected to be related to CC-90009. This included sepsis in 3 (3.7%) subjects each. All other TEAEs leading to death occurred in 1 subject each (1.2%): bacterial sepsis; Klebsiella sepsis, pneumonia, sepsis syndrome, and Stenotrophomonas sepsis.

The categorical term of sepsis includes AE preferred terms of bacterial sepsis, Escherichia sepsis, Klebsiella sepsis, neutropenic sepsis, sepsis, sepsis syndrome, septic shock, and Stenotrophomonas sepsis. Twenty-four (29%) subjects experienced sepsis in this study: 18 (25%) subjects were in Part A and 6 (75%) subjects were in Part B in the R/R AML cohort. No sepsis was reported in the 2 subjects enrolled in the R/R HR-MDS cohort in Part B. The rate of sepsis in the Part B R/R AML cohort (75%, 6 of 8 subjects) was higher than the overall rate (25%, 18 of 72 subjects) of sepsis from Part A Dose Escalation of this study, and it was higher than the rate (18%, 2 of 11 subjects) of sepsis among subjects receiving the same dose of CC-90009 on the same schedule in Part A. In Part A, the incidence of sepsis is 15%, 29% and 36% among subjects receiving consecutive daily CC-90009 doses of 2.4 mg and below (n = 13), 3.0 mg (n = 24), and 3.6 mg and above (n = 25), respectively, demonstrating a potential dose-dependent relationship between CC-90009 and the development of sepsis. There was no sepsis reported in cohorts with

CC-90009 dosed at shorter step intervals (ie, when CC-90009 is dosed on cycle Days 1-3 followed by Days 8-10), and this schedule is not being pursued based on a lack of objective responses.

An exploratory analysis of CC-90009 plasma exposures in subjects who developed sepsis showed that exposures were elevated by approximately 1.56-fold compared to subjects who did not develop sepsis. Additionally, subjects who received strong inhibitors of CYP3A4 enzyme (N=20) showed that exposures were elevated by approximately 1.8-fold (median dose-normalized AUC_{24} = 192 ng.hr/mL) compared to subjects who did not receive strong CYP3A4 inhibitors or received moderate CYP3A4 inhibitors (N = 59, median AUC_{24} = 106 ng.hr/mL), suggesting a potential drug-drug interaction of CC-90009 with strong inhibitors of CYP3A4.

Comprehensive analysis of available PK, PD, efficacy, safety, and tolerability data led to the development of a strategy to reduce the risk of sepsis. The strategy includes evaluating doses of CC-90009 lower than 3.6 mg and schedules longer than 5 days that had been selected as the dose level for the Part B Dose Expansion. New Part B R/R AML and R/R HR-MDS cohorts will be enrolled at CC-90009 dose levels of 2.4 mg Days 1-7 and 3.0 mg Days 1-7. The strategy also includes dose reduction of CC-90009 for subjects receiving concomitant strong CYP3A4 inhibitors.

Please refer to the CC-90009 IB for additional PK summary parameters by individual dose levels and for more detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and AE profile of CC-90009.

1.2.4 Safety Monitoring Plan

Experience with CC-90009 in humans is limited to two ongoing studies, CC-90009-AML-001 (a first-in-human study of CC-90009 monotherapy in subjects with R/R AML or R/R HR-MDS) and CC-90009-AML-002 (a Phase 1b study of CC-90009 in combination with anti-leukemia agents in subjects with AML), and the most extensive clinical information comes from the CC-90009-AML-001. Therefore, the efficacy and safety profiles of CC-90009 in humans are not yet fully established. Potential toxicities for CC-90009 are being identified based on data from the two ongoing clinical studies, nonclinical studies, and literature review for other CBRN binding agents. As discussed in Section 1.2.2, clinical pathology findings in cynomolgus monkey studies have included decreased body weights, alterations in serum chemistry parameters, and decreases in peripheral blood lymphocytes, neutrophils, platelets, and reticulocytes. Histopathologic findings included variable changes in lymphoid organs and decreases in bone marrow cellularity.

Subjects will be monitored for possible toxicity through standard and specialized laboratory tests including complete blood counts (CBC), prothrombin time (PT)/partial thromboplastin time (PTT)/international normalized ratio (INR), and serum chemistries. Prophylaxis is allowed for potential secondary infections due to immunosuppression.

Alterations in serum chemistry parameters in the cynomolgus monkey studies included decreased protein, albumin, and calcium. Monitoring in the clinic will include standard serum chemistry panels and calcium metabolism monitoring (serum calcium, albumin, magnesium [Mg], phosphorous, parathyroid hormone [PTH], total procollagen type 1 N-terminal propeptide [P1NP], β-C-terminal telopeptide [β-CTx], and urine calcium/creatinine ratio). Subjects will be admitted

as inpatients in Cycle 1 and will either be admitted as inpatients or treated in a Limited Stay Unit (LSU) throughout the administration of CC-90009 in Cycle ≥ 2. Additionally, subjects who have grade ≥ 2 hypocalcemia during any cycle should be admitted as inpatients throughout administration of CC-90009 in subsequent cycles and be monitored as in Cycle 1 (an exception can be made for subjects with grade 2 hypocalcemia lasting less than 24 hours that recovers without IV calcium [eg, calcium gluconate or calcium chloride] after discussion with the Celgene medical monitor). Subjects who dose escalate will be admitted as inpatients in the first cycle of the higher dose. Calcium, calcitriol, and vitamin D supplements will be taken starting at least 3 days prior to Day 1 of each cycle and continuing until ≥ 3 days after the last dose of CC-90009 in each cycle (eg, ≥ Day 8 when CC-90009 is administered on Days 1 to 5). Guidelines for the management of hypocalcemia are provided in Section 7.2.13.2.

Standard eligibility criteria are included to ensure acceptable baseline organ function and lack of clinically significant comorbid disease (refer to Sections 4.2 and 4.3).

Subjects are at risk for tumor lysis syndrome (TLS). Eligibility criteria require normal renal function and baseline serum chemistries (uric acid, potassium, lactate dehydrogenase [LDH]) consistent with a lower risk of TLS. Subjects will be closely monitored for laboratory changes suspicious for TLS on Days 1 through 5 in Cycle 1. Hospitalization for management of suspected TLS with hypouricemic agents, IV hydration, and correction of electrolyte abnormalities is recommended (refer to Section 7.2.13.1 and Appendix I).

Infusions of a chemotherapeutic agent may cause infusion reactions ranging from localized injection site reactions to severe and life-threatening infusion reactions. Subjects should be monitored closely during the administration of CC-90009 and for at least one hour after completion. Guidelines for management of infusion reactions are provided in Section 7.2.13.7.

Although CC-90009 modulates cereblon, the same molecular target of the IMiD™ immunomodulatory drugs (thalidomide and its analogues, eg, lenalidomide, pomalidomide), CC-90009 is mechanistically different. Interaction of CC-90009 with cereblon does not lead to degradation of the same set of proteins as the IMiD™ immunomodulatory drugs. Reproductive studies have not been conducted with CC-90009. Subjects will be required to follow the CC-90009 Pregnancy Prevention Plan (PPP) for Celgene Clinical Trials as described in Section 6.1.1 and Appendix L.

Subjects given CC-90009 at daily doses ≥ 3.6 mg will be administered concurrent dexamethasone per Section 7.2. Subjects enrolled on other dose levels may be administered corticosteroid premedication as per SRC recommendation (eg, at the 3.0 mg dose level on the Days 1-7 and Days 1-10 schedules).

Subjects may be at risk for hypotension, infections (eg, sepsis), and other potential hematological and non-hematological toxicities. Subjects will be closely monitored for possible toxicity throughout the study by physical exam, vital sign and AE collection, through standard and specialized laboratory tests including hematology and serum chemistry labs and electrocardiogram (ECG). Refer to Section 7.2.13.4 for guidelines on infection prophylaxis, Section 7.2.13.8 for

guidelines on management and grading of hypotension, and Table 4 through Table 7 (D1-5 schedule), Table 31 through Table 38 (D1-3/8-10, D1-7, and D1-10 schedules).

Exploratory analyses of CC-90009 plasma exposures indicated a potential drug-drug interaction of CC-90009 with strong inhibitors of CYP3A4. Please refer to Section 7.2.15 for guidelines on dose modifications of CC-90009 for concomitant use of strong CYP3A4 inhibitors.

The global coronavirus disease 2019 (COVID-19) pandemic has been identified as a potential risk to clinical trial subjects in general. Immunocompromised patient populations such as those with R/R AML and HR-MDS may be more susceptible to infections, including SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infections. In addition, the potential impact of CC-90009 administration on the frequency or severity of SARS-CoV-2 infections in subjects with R/R AML or HR-MDS are currently unknown. To mitigate this potential risk, RT-PCR testing for SARS-CoV-2 infection will be mandatory for all subjects. Subjects with recent or acute SARS-CoV-2 infections will be excluded (Section 4.3) or delay start of treatment as defined in Section 6.1. If a subject has a confirmed SARS-CoV-2 infection while on study treatment, dose delay or interruption of study treatment is required as described in Section 7.2.13.4.1. An exploratory analysis of the impact of SARS-CoV-2 serologic status on subjects receiving CC-90009 may be performed.

The study has been designed with study visits that allow for close monitoring of subjects' safety throughout the clinical trial (Section 6), and subjects are encouraged to contact the investigator if an intercurrent illness develops between study visits. Testing for COVID-19 to inform decisions about clinical care during the study should follow local standard practice. Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in subjects receiving CC-90009 is unknown.

Based on the current knowledge of the safety profile of CC-90009 available from non-clinical and clinical studies, and considering the safety monitoring and management, dosing, precautions, and guidance specified in the CC-90009-AML-001 protocol and the Investigator's Brochure, the benefit-risk balance is assessed as acceptable for continuing with the current clinical study in AML and HR-MDS subjects with limited treatment options.

1.3 Rationale

1.3.1 Study Rationale and Purpose

CC-90009 is a new IP that has a strong biological rationale for the treatment of subjects with AML and HR-MDS (refer to Section 1.2). This Phase I study is designed to determine the safety and tolerability of CC-90009 as well as evaluating the biologic and clinical activity in subjects with R/R AML or R/R HR-MDS. The study will be conducted in two parts: dose escalation (Part A) and dose expansion (Part B).

1.3.2 Rationale for the Study Design

In Part A, a modified accelerated titration design (Simon, 1997) will be used to establish initial safety and tolerability and identify tolerable dosing schedules for expansion in Part B. The

modified accelerated titration design allows for fewer subjects to be treated at a lower CC-90009 dose that is potentially not efficacious. Escalations will be decreased from 100% to ≤ 50% when ≥ 2 subjects experience a CC-90009-related Grade ≥ 2 adverse event in the dose-limiting toxicity (DLT) window (may be different cohorts), or ≥ 1 subject experiences a DLT within the DLT window. At that time the current cohort and all subsequent cohorts will be expanded enrolling 3 to 6 subjects using a traditional 3+3 design (Storer, 1989). Refer to Figure 2 for sample dose escalation schemes and Section 7.2 for additional dose escalation information.

One or more dosing regimens may be selected for cohort expansion in Part B to obtain additional safety and efficacy information for larger cohorts of subjects (up to approximately 20 in each arm). At least one cohort will include R/R AML subjects, including subjects who relapse after allogeneic HSCT, who are in second or later relapse, who are refractory to initial induction or re-induction treatment, who are refractory to or relapsed after hypomethylating agents (HMA failure defined as primary progression or lack of clinical benefit after a minimum of 6 cycles or unable to tolerate HMA due to toxicity), or who relapse within 1 year of initial treatment (excluding those with favorable-risk status) and at least one cohort of relapsed or refractory HR-MDS subjects will be enrolled in Part B at the dose/schedule selected by the SRC based on available data from Part A.

1.3.3 Rationale for Dose, Schedule, and Regimen Selection

Based on the findings in the pivotal repeat-dose toxicity studies, the cynomolgus monkey is the more sensitive species for CC-90009-mediated toxicities, and therefore, should be used for estimating a starting dose in the initial clinical study with CC-90009. In the definitive 28-day repeat-dose toxicity study in monkeys, daily treatment at 0.03 mg/kg was identified as the HNSTD.

The highest dose of 0.3 mg/kg/day administered for a total of 10 days (Days 1 to 5 and Days 15 to 19) was considered to be severely toxic based on adverse clinical condition and bone marrow toxicity. The adverse clinical condition was determined in a subsequent study to be related to the hypocalcemic effect at this dose, could be alleviated by calcium and vitamin D supplementation, and was rapidly reversible following discontinuation of CC-90009. The hypocalcemic effect is monitorable in humans and calcium, calcitriol, and vitamin D supplementation will be employed in this study prior to and concomitant with study drug dosing.

At the mid-dose of 0.1 mg/kg/day, the hypocalcemic effect was slight (-11 to -17%) after 4 weeks of daily dosing and was not considered adverse. Although marked bone marrow hypocellularity was observed at the end of the 28-day dosing period and was considered as severely toxic, the same dose of 0.1 mg/kg/day given daily on Days 1 to 7 and Days 12 to 22 in the 28-day exploratory toxicology study only resulted in a slight decrease in bone marrow cellularity. Therefore, when given intermittently for 7 days every two weeks, this dose was not severely toxic. Further supporting intermittent dosing, the highest dose of 0.3 mg/kg/day administered daily for 5 days every 2 weeks resulted in slight to moderate hypocellularity that recovered within 28 days in all but one animal. The recovery at this dose level was likely delayed by the second 5-day dosing period on Days 15 to 19. Although this dose was severely toxic based on the bone marrow findings, bone marrow hypocellularity is common in standard of care AML therapy, such as 7+3 induction

chemotherapy, and is an acceptable toxicity in this population as long as hematopoietic recovery is observed following treatment discontinuation.

Based on the monkey study observations, the initial schedule to be evaluated for CC-90009 is once daily (QD) dosing on Days 1 to 5 of 28 day cycles for up to 4 cycles. This schedule is designed to allow short intensive cytotoxic therapy followed by a bone marrow recovery period and is consistent with standard induction therapy paradigms in AML. Initial dosing only on Days 1 to 5 mitigates the risk of delayed bone marrow recovery observed with the second 5-day dosing period (Days 15 to 19) at 0.3 mg/kg in monkeys. This initial schedule is also selected to mitigate hypocalcemia as the effect became adverse when the 0.3 mg/kg animals were dosed for longer than 5 days. The initial schedule of CC-90009 given on Days 1 to 5 supports an initial human starting dose of 0.3 mg, which provides an approximately 20-fold margin below the severely toxic dose (STD) of 0.3 mg/kg given on Days 1 to 5 and Days 15 to 19 in the 28-day monkey study.

The starting doses calculated based on doses tested in the 28-day monkey studies and the ICH S9 recommended 6-fold margin in oncology patients are given in Table 1. Overall, CC-90009 exhibits an acceptable safety profile in preclinical species for an oncology clinical candidate, and the toxicology program for CC-90009 adequately supports the conduct of clinical trials in oncology patients.

After review of the data from the first 5 dose levels, an additional schedule of CC-90009 administered once daily on Days 1-3 and Days 8-10 of each 28 day schedule (D1-3/D8-10) may be explored. The rationale for this schedule is based on the clinical experience to date using once daily dosing on Days 1 to 5 of 28 day cycles. Study drug-related non-hematologic toxicities were mostly observed during the later dosing days (Days 3-5) and were rapidly reversed once dosing ended. Shorter intervals of dosing (ie, 3 days) could mitigate non-hematologic toxicity. Meanwhile, the observed blast reduction with Days 1-5 dosing persisted through Day 8, but, in several patients, blasts recovered between Days 15- 28. Therefore, repeat dosing for 3 days on Days 8-10 could allow further blast reduction while still allowing a study drug-free interval of > 2 weeks for recovery from bone marrow myelosuppression. Finally, if rapid death of leukemic blasts is associated with non-hematologic toxicity (eg, tumor lysis syndrome or cytokine mediated inflammatory response/hypotension), the Days 1-3 and Days 8-10 schedule could mitigate this toxicity by triggering a slower initial blast reduction either via the shorter interval of dosing or through the use of a lower dose on Days 1-3 (see example in Figure 3).

After review of the clinical data where CC-90009 has been evaluated in consecutive daily dosing on the Days 1-5 (D1-5) and intermittent (D1-3/8-10) schedules, extended consecutive days of dosing may be explored (eg, Days 1-7 and/or Days 1-10). The rationale for increasing the days of dosing to either Days 1-7 or Days 1-10 schedules stems from review of the kinetics of peripheral blast decrease and timing of rebound as well as PD findings (eg, GSPT1 decrease and recovery). On 07 June 2019, the SRC recommended extending the number of dosing days to Days 1-7 as a future cohort in dose escalation. This was partly based on the observation that in some patients with high peripheral blood leukemic blasts, the Days 1-5 dosing was suboptimal. In these subjects, the blasts were still dropping but had not reached nadir by the last consecutive daily dose on Day 5. Therefore, extending the dosing days at a dose level that was tolerated on the Days 1-5 schedule

would have potential to further deepen the leukemic blast reduction. Study drug-related non-hematologic toxicities (eg, tumor lysis syndrome or cytokine mediated inflammatory response/hypotension) have been manageable with the implementation of concurrent dexamethasone for CC-90009 dosing for the current 3.6 mg dose levels. Decision to test the extended consecutive days of dosing (ie, Days 1-7 and Days 1-10 schedules) will be based on SRC review of toxicity, PK profiles, and PD findings from the Days 1-5 and Days 1-3/8-10 dosing schedules.

Table 1: Starting Doses in Humans Based on the Doses Tested in the 28-day Monkey Studies with CC-90009

Monkey Dose and Schedule (mg/kg/day)	HED (mg/kg)[a]	HED (mg/day)[b]	Safety Factor[c]	HED/Safety Factor (mg/day)	Human Starting Dose (mg/day)[d]	Predicted Exposure Multiple Based on Monkey Dose (AUC, C_{5min})[e]
0.03 QD for 28 days (HNSTD)	0.0097	0.6	6	0.1	0.1	6x, 15x
0.1 x 7 days Q2W for 28 days (HNSTD)	0.032	1.92	6	0.3	0.3	11x, 15x
0.3 x 5 days Q2W for 28 days (STD)	0.097	5.8	6	1	1	7x, 15x

Abbreviations: AUC = area under the concentration-time curve; C_{5min} = plasma concentration of the drug at 5 minutes postdose; HED = human equivalent dose; HNSTD = highest non-severely toxic dose; Q2W = every 2 weeks; QD = every day; STD = severely toxic dose.

[a] Value calculated using HED conversion factor from the July 2005 FDA Guidance for Industry: "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (FDA, 2005).

[b] Value calculated for a 60-kg human.

[c] Value from ICH S9 Guideline: "Nonclinical Evaluation for Anticancer Pharmaceuticals" (ICH, 2009).

[d] Using the allometry-derived plasma clearance (18.9 L/hr) and volume of distribution (1.44 L/kg) estimates, the predicted steady state $C_{5\ min}$ and systemic exposure (AUC_{24hr}) of CC-90009 following daily administration of a 0.3 mg IV infusion dose in a 60-kg human are 3.4 ng/mL and 15.7 ng·hr/mL, respectively.

[e] Predicted exposure multiple equals animal value divided by predicted human value at each corresponding human starting dose.

Refer to the Investigator's Brochure for detailed information.

1.3.4 Rationale for Dose and Dosing Schedule in Part B Dose Expansion

Data generated from Part A Dose Escalation of the study suggest a manageable safety profile and encouraging preliminary clinical activity of CC-90009 in subjects with R/R AML (Section 1.2.3). At the completion of Part A Dose Escalation, a total of 72 subjects were treated with CC-90009. Preliminary safety and efficacy data are available for these 72 subjects treated in Part A. All data were assessed both internally and by SRC, and a non-tolerated dose (NTD) was successfully determined on 3 of the 4 schedules evaluated. The Days 1-3/8-10 schedule was not pursued further due to lack of efficacy prior to declaring either a maximum tolerated dose (MTD) or NTD. Based

on the observed DLTs and definitions of NTD and MTD set in the protocol, the SRC declared 3.0 mg Days 1-5 without dexamethasone premedication and 3.6 mg Days 1-5 with dexamethasone premedication as MTDs on the Days 1-5 schedule. After further review of preliminary safety, anti-leukemic activity and PK/PD data from all dose levels, the SRC recommended 3.6 mg Days 1-5 with dexamethasone premedication as the dose and schedule to be expanded for the initial cohorts of R/R AML and R/R HR-MDS subjects in Part B.

Overall, evidence of anti-leukemic activity (decreases in bone marrow and/or peripheral blasts) was seen in subjects treated with CC-90009 at 1.2 mg and above with a trend to deeper and more sustained reductions at the highest dose levels. Objective responses were observed in cohorts with 5 or more days of continuous dosing at 3.0 and 3.6 mg with a trend for better efficacy at 3.6 mg. A higher dose of 4.5 mg on this schedule was not tolerated.

Attempts to shorten the dosing schedules with intermittent dosing of either 3.0 mg or 3.6 mg on Days 1-3 and 8-10 were unsuccessful due to lack of efficacy. While these regimens were tolerated, they were not pursued based on lack of objective response: this intermittent dosing schedule did not sufficiently suppress leukemic blasts, which increased in the peripheral blood on non-dosing days.

Dosing schedules with more than 5 consecutive days (3.6 mg Days 1-7 and 3.0 mg Days 1-10) were not well tolerated at dose levels tested based on DLTs using the current hypotension grading in Protocol Amendment 7 (Table 12), interruptions and missed doses. However, responses were noted in both of these dose levels.

In Part A, at the selected Part B dose and schedule of 3.6 mg Days 1-5 with dexamethasone premedication, all subjects received 100% of the planned dose when given dexamethasone premedication and no subject experienced dose-limiting hypotension. Two (25%) subjects achieved objective responses (CR and CRi).

Selection of 3.6 mg as compared to 3.0 mg on the Days 1-5 schedule was further supported by PK and PD data. PK of CC-90009 was evaluated after single- and repeat-dose administration during the first dosing cycle. Preliminary results have demonstrated dose-dependent exposure increases in CC-90009 across the dose range of 0.6 mg to 4.5 mg. The PK profile is generally consistent across doses and dosing schedules. Preliminary analysis of exposure-efficacy and exposure-safety correlations from Part A data suggest that lower daily exposure (as measured by AUC_{24}) achieved by 3.6 mg relative to 4.5 mg would be anticipated to mitigate risk of higher-grade hypotension, while 3.6 mg relative to 3.0 mg would be anticipated to lead to greater likelihood of achieving systemic exposures that are considered sufficient for clinical response in a greater proportion of subjects.

PD biomarkers for GSPT1 and downstream pathway markers were assessed in evaluable subjects. A dose-dependent decrease in GSPT1 levels in peripheral blood blasts and T cells was observed, with a maximal >90% decrease observed for higher dose levels. At the selected Part B dose of 3.6 mg, the degradation of GSPT1 achieved the desired threshold within 24 hrs in most subjects and was maintained at this level throughout the dosing period.

In light of dose-related pharmacokinetics, evidence of deep GSPT1 degradation and on-target activity, promising anti-leukemic activity, and acceptable safety and benefit-risk balance, the SRC recommended proceeding to Part B Dose Expansion at the MTD of 3.6 mg with dexamethasone premedication on Days 1-5 in patients with R/R AML and R/R HR-MDS.

After an initial 8 R/R AML subjects enrolled in Part B at dose level 3.6 mg Days 1-5 with dexamethasone premedication, a high rate of sepsis (75%) was observed in this cohort, and enrollment to both R/R AML and R/R HR-MDS cohorts were paused. There were no significant findings on demographic and baseline characteristics of R/R AML subjects enrolled at the same dose level (CC-90009 3.6 mg D1-5 with or without dexamethasone premedication) in Part A Dose Escalation (n = 11) and Part B Dose Expansion (n = 8). In both Parts A and B, preliminary analyses of pharmacokinetic data demonstrated increased CC-90009 exposure (1.56-fold) among subjects who developed sepsis as well as increased exposure (1.8-fold) among subjects who received concomitant strong CYP3A4 inhibitors. Preliminary modeling of exposure-sepsis and exposure-clinical response relationships indicated that cumulative exposure of CC-90009 (AUC_{CUM}) was less predictive of sepsis than daily exposure (odds ratio [95% confidence interval]: 2.55 [1.17–6.65] for AUC_{CUM} as the predictor vs. 3.84 [1.35–13.35] for AUC_{24} as the predictor) and that AUC_{CUM} was more predictive of clinical response than AUC_{24} (odds ratio [95% Confidence Interval]: 5.06 [1.61–21.16] for AUC_{CUM} vs. 3.04 [0.97–13.07] for AUC_{24}). Comprehensive analysis of available PK, PD, efficacy, safety, and tolerability data led to the development of a strategy to reduce the risk of sepsis. The strategy includes evaluating doses of CC-90009 lower than 3.6 mg and schedules longer than 5 days that had been selected as the dose level for the Part B Dose Expansion. New cohorts in Part B will be enrolled at CC-90009 dose levels of 2.4 mg Days 1-7 and 3.0 mg Days 1-7. R/R AML and R/R HR-MDS subjects will be pooled in each cohort with 6 to 40 subjects enrolled in each cohort, including up to 20 subjects with R/R AML and up to 20 subjects with R/R HR-MDS in each cohort. The strategy also includes dose reduction of CC-90009 for subjects receiving concomitant strong CYP3A4 inhibitors. The new Part B cohorts will enroll subjects in parallel. Up to 6 subjects per cohort will be initially enrolled as a safety run-in. The SRC will assess tolerability of the dose and schedule for these initial subjects that completed at least one cycle of study treatment based on the Part A stopping criteria (Section 7.2.8) and recommend further expansion of one or more cohorts. The expanded cohort(s) will be monitored for the excess toxicities including sepsis utilizing the non-binding Bayesian stopping criterion on a continuous basis (Section 9.9.3). Subjects of R/R AML and R/R HR-MDS enrolled in the expansion cohorts will be pooled for analysis of safety, PK, and PD. The SRC will continue to review safety and preliminary efficacy data regularly throughout the study and make recommendations about study continuation, cohort continuation, and dose modification, as appropriate.

1.3.5 Rationale for Pharmacodynamics and Potential Predictive Biomarkers

The therapeutic hypothesis for CC-90009 activity in AML and MDS is that CBRN-dependent substrate degradation and induction of UPR preferentially kill leukemic cells, and a therapeutic index of 2- to 5-fold over normal hematopoietic stem cells can be achieved with intermittent dosing. CC-90009 binding to the $CRL4^{CRBN}$ complex promotes ubiquitination and degradation of

substrates. Substrate degradation by CC-90009 leads to activation of the UPR pathway and induces apoptosis in AML cells.

CC-90009 is broadly active at killing leukemic cells in ex-vivo cultures of primary bone marrow cells from AML patients, while a spectrum of sensitivities have been observed across a 20 cell line AML panel. In vitro studies in AML cell lines show that the extent of CRBN-dependent substrate reduction by CC-90009 is predictive of apoptosis sensitivity.

Blood will be collected predose and postdose for the purpose of measuring PD markers of CC-90009 activity. Priority PD endpoints include quantification of CBRN substrates and quantification of markers of UPR and nonsense-mediated decay (NMD). A portion of bone marrow tissue (biopsy and aspirate), collected before and during treatment, will also be utilized for evaluation of PD endpoints.

Ongoing studies are evaluating the exposure-response relationships to PD and efficacy endpoints to model the dose and exposure profile predicted to affect biologic and clinical activity with CC-90009 therapy. This modeling along with PD data collected will be used to support decisions about dose and schedule during the study. In the expansion phase of the study, the relationship between PD markers and safety and/or efficacy will be further explored in both AML and HR-MDS cohorts.

No patient selection hypotheses have been developed for prospective clinical testing at this time. Correlative analyses of molecular characteristics of AML cell lines with differential sensitivities to CC-90009 are ongoing to generate such hypotheses. Further, expanded evaluations of ex vivo treated primary AML bone marrow samples, with molecular characterization, have been initiated. For the purpose of retrospective evaluation of potential predictive markers of CC-90009 efficacy, bone marrow and/or blood samples may be characterized in molecular and cellular assays, potentially including, but not limited, to cytogenetics, gene variants analyses (eg, gene sequencing), messenger ribonucleic acid (mRNA)/microRNA expression (eg, RNA sequencing), functional assays (eg, engraftment potential), clonal architecture, ex vivo sensitivity assays with CC-90009, and immunophenotyping.

2 STUDY OBJECTIVES AND ENDPOINTS

Table 2: Study Objectives

Primary Objectives
The primary objectives of the study are: • To determine the safety and tolerability of CC-90009. • To define the non-tolerated dose (NTD), the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of CC-90009.
Secondary Objectives
The secondary objectives are: • To provide information on the preliminary efficacy of CC-90009 in R/R AML and R/R HR-MDS. • To characterize the PK of CC-90009 in plasma and urine.
Exploratory Objectives
The exploratory objectives are: • To explore the relationship between systemic exposure of CC-90009 and measures of toxicities, effectiveness, and PD biomarkers. • To evaluate molecular and/or cellular markers in the bone marrow and blood that may be predictive of efficacy with CC-90009. • To characterize the PK of hydroxypropyl-beta cyclodextrin in plasma and urine. • To assess the impact of SARS-CoV-2 serologic status on subjects with R/R AML or HR-MDS receiving CC-90009. Data from exploratory objectives may not be included in the Clinical Study Report.

Table 3: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	Safety endpoints	DLTs, NTD, and MTD evaluated using the NCI CTCAE criteria, Version 4.03. Adverse events, including treatment-emergent adverse events (TEAEs), laboratory assessments, vital signs, ECG results, ECOG performance status, LVEF assessments, physical examinations, and vital signs.	Screening until 28 days after the last dose of CC 90009 for each subject during both dose escalation and expansion phases.
Secondary	Preliminary efficacy	Determined by response rates of AML by disease response criteria.	Dose escalation and dose expansion; throughout Treatment Period and the Follow-up Period (refer to Sections 6.3.2 and 6.3.3)
		Overall survival, relapse-free survival, progression-free survival, event-free survival, duration of remission, duration of response, and time to remission/response for AML subjects.	
		Determined by response rates of HR-MDS by disease response criteria.	Dose escalation and dose expansion; throughout Treatment Period and the Follow-up Period (refer to Sections 6.3.2 and 6.3.3) of Part B only
		Overall survival, relapse-free survival, progression-free survival, event-free survival, duration of remission, duration of response, time to AML transformation, and time to remission/response for HR-MDS subjects.	
	PK endpoints	Noncompartmental PK parameters of CC-90009 in plasma and urine including observed maximum concentration (C_{max}), area under the plasma concentration time-curve from time 0 to 24 hours postdose (AUC_{24}), time to peak (maximum) plasma concentration (t_{max}), terminal half-life ($t_{1/2}$), total body clearance of the drug from the plasma (CL), and volume of distribution at steady-state (V_{ss}), % dose excreted in urine as unchanged (F_e), and renal clearance (CL_R).	Dose escalation and/or dose expansion, when feasible
Exploratory	PD endpoints	• CRBN substrate protein level • RNA and/or protein levels of markers of unfolded protein response and non-sense mediated decay (NMD) of RNA • Blasts in bone marrow and peripheral blood • Leukemic stem cell quantification in bone marrow	Dose escalation and dose expansion; throughout Treatment Period and the Follow-up Period (refer to Sections 6.3.2 and 6.3.3)
	Predictive/ prognostic endpoints	• Standard AML diagnostics (cytogenetics, FISH, and molecular [eg, KIT, FLT-3, NPM1, CEBPα]) • Expanded gene sequence analysis (myeloid cancer gene panel) • Gene expression (eg, RNA sequence) • Protein expression of mechanism markers (eg, CRBN substrates, CRBN, endoplasmic reticulum stress markers) • Minimal residual disease (MRD)	Dose escalation and dose expansion; throughout Treatment Period and the Follow-up Period (refer to Sections 6.3.2 and 6.3.3)

Table 3: Study Endpoints

Endpoint	Name	Description	Timeframe
	PK endpoints	• Clinically relevant covariates of PK parameters • Profile of CC-90009 metabolites in plasma • Exposure-response relationships • Noncompartmental PK parameters of HPBCD in plasma and urine including C_{max}, AUC_{24}, t_{max}, $t_{1/2}$, CL, V_{ss}, F_e, and CL_R.	Dose escalation and/or dose expansion
	SARS-CoV-2 serologic status	• Exploratory measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG) from serum samples collected at baseline and specified timepoints.	Dose expansion

Abbreviations: AML = acute myeloid leukemia; CEBPα = CCAAT/enhancer binding protein (c/EBP), alpha; CRBN = cereblon; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = eastern cooperative oncology group; FISH = fluorescence in situ hybridization; FLT-3 = FMS-like tyrosine kinase 3; HPBCD = Hydroxypropyl beta-cyclodextrin, IgG = immunoglobulin G; KIT = stem cell factor receptor; LVEF = left ventricular ejection fraction; MTD = maximum tolerated dose; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NPM1 = nucleophosmin 1; NTD = non-tolerated dose; PD = pharmacodynamic; PK = pharmacokinetic; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus.

3 OVERALL STUDY DESIGN

3.1 Study Design

Study CC-90009-AML-001 is an open-label, Phase 1, dose escalation and expansion, first-in-human clinical study of CC-90009 in subjects with relapsed or refractory AML (Appendix B) or in subjects with relapsed or refractory higher-risk MDS (Appendix E and Appendix G). The dose escalation part (Part A) of the study will evaluate the safety and tolerability of escalating doses of CC-90009, administered intravenously, and determine the MTD of CC-90009. In Part A, two formulations were tested. The expansion part (Part B) will further evaluate the safety and efficacy of CC-90009 administered at or below the MTD in selected expansion cohorts of up to approximately 20 evaluable subjects in each disease indication (R/R AML and R/R HR-MDS) in order to determine the RP2D. One or more dosing regimens may be selected for cohort expansion (at a minimum, one in R/R AML and one in R/R HR-MDS). MDS subjects will only be enrolled during Part B. Parts A and B will consist of 3 periods: Screening, Treatment, and Follow-up. Leukemia response will be determined by the Investigator. Disease assessment will be based on the International Working Group (IWG) Response Criteria in AML (Cheson, 2003; refer to Appendix C). MDS response will be based on the IWG Response Criteria for Myelodysplasia (Cheson, 2006; refer to Appendix F).

Screening Period

The Screening Period starts 28 days prior to first dose of CC-90009. The informed consent document (ICD) must be signed and dated by the subject and the administering staff prior to the start of any other study procedures. All screening tests and procedures must be completed within the 28 days prior to the first dose of CC-90009.

Treatment Period

In the Treatment Period, CC-90009 will be administered intravenously QD on Days 1-5 of each cycle for up to 4 cycles in the absence of disease progression (as defined in Section 6.4), relapse, unacceptable toxicity, or subject/physician decision to withdraw. Modified dosing schedules (eg, increasing from 5 consecutive days to up to 7 or 10 consecutive days of dosing or increasing infusion length) may be evaluated in additional cohorts, if necessary, based on toxicity, PK profiles, and PD findings. An additional schedule of CC-90009 administered once daily on Days 1-3 and Days 8-10 of each 28 day cycle will be explored. Tables of Events for the alternate dosing schedules (eg, D1-3/D8-10, D1-7, and D1-10 Dosing Schedules) are located in Appendix K and Appendices M-O. Those who demonstrate benefit from treatment without unacceptable toxicity (any complete remission [CR], morphologic leukemia-free state [MLFS], partial remission [PR], or stable disease with discussion with Medical Monitor) may continue treatment beyond Cycle 4 until loss of that benefit, unacceptable toxicity, or subject/physician decision to withdraw.

All subjects will be required to start calcium, calcitriol, and vitamin D supplementation at least 3 days prior to Day 1 of each cycle and continue until ≥ 3 days after the last dose of CC-90009 in each cycle (eg, ≥ Day 8 when CC-90009 is administered on Days 1-5, ≥ Day 10 when CC-90009 is administered on Days 1-7, or ≥ Day 13 when CC-90009 is administered on Days 1-3/Days 8-10 or Days 1-10).

In Cycle 1 of Part A, a bone marrow evaluation will be performed on Days 28 (± 3 days). Based on the Day 28 bone marrow evaluation, subjects with hypoplastic bone marrow, without evidence of persistent leukemia, who have Grade ≥ 3 neutropenia will be followed for an additional 2 weeks for safety monitoring in Cycle 1 (total duration of 42 days; refer to Figure 1). An additional bone marrow assessment will be performed at the time of hematologic recovery or Day 42 (± 3 days). Thus, in Part A, the window for evaluation of DLT during Cycle 1 will be up to 42 days (28 or 42 days). In Part B, Cycle 1 will be 28 days in length. Cycles ≥ 2 will be 28 days in length. Subsequent cycles should start ≤ 7 days following the last day of the previous cycle. Permitted treatment delays are described in Section 7.2.12.

Retreatment will be allowed for subjects who transition from the treatment period to the follow-up period of the study in CR, CRi or Morphologic CR with partial hematologic recovery (CRh) and who have relapsed after a prolonged remission (eg, > 6 months). The subject cannot have had another systemic anti-cancer therapy upon relapse. The subject can be considered for retreatment after confirmation that they continue to meet the eligibility criteria for the study and after discussion with the Sponsor medical monitor. Subjects who discontinue treatment due to adverse event or disease progression are not eligible for retreatment. Subjects will only be considered DLT evaluable during the first cycle of their initial enrollment in Part A (Section 7.2.3). The subject will not be re-considered in the efficacy evaluation (Section 9.1).

Follow-up Period

In the Follow-up Period, all subjects will be followed for 28 days (± 3 days) after the last dose of CC-90009 for safety.

Subjects without documented progression of disease (or relapse) will have efficacy evaluations of complete blood counts and peripheral blood smears performed every subsequent 8 weeks (± 1 week) for the 1st year and every 12 weeks (± 2 weeks) for the 2nd year or until progression of disease (or relapse), initiation of a new anticancer therapy, withdrawal of consent from the study, death, or the End of Trial, whichever comes first. A bone marrow evaluation will be completed at the end of the 1st year and as clinically indicated during the Follow-up Period.

All subjects will be followed for survival follow-up according to the schedule for the efficacy long term follow-up for up to 2 years or until death, lost to follow-up, or the End of Trial, whichever occurs first. Survival follow-up may be conducted by record review (including public records) and/or telephone contact with the subject, family, or the subject's treating physician.

Part A-Dose Escalation

During the escalation phase (Part A), a modified accelerated titration design (Simon, 1997) will be used to establish initial toxicity. Cohorts of one or more subjects each will be administered CC-90009 at doses that will increase in 100% increments per cohort until ≥ 2 subjects experience a CC-90009-related Grade ≥ 2 adverse event (AE) in the DLT window (may be different cohorts), or ≥ 1 subject experiences a DLT within the DLT window. At that time the current cohort and all subsequent cohorts will be expanded enrolling 3 to 6 subjects. A dose escalation schedule with dose increments not to exceed 50% will concurrently be initiated in order to establish the NTD and MTD (refer to Section 7.2.2). The initial dose will be 0.3 mg. Sample dose escalation schemes for Part A are shown in Figure 2. At the study start an initial formulation (Gen 1) was utilized and during dose escalation a second formulation (Gen 2b) was introduced to replace Gen 1. The DMA residual solvent in the Gen 1 CC-90009 formulation must not exceed the ICH PDE limits in order to proceed with dose escalation cohorts above a daily CC-90009 dose of 2.4 mg. Gen 2b CC-90009 formulation is permitted at daily doses up to 20 mg. The Gen 2b formulation was introduced at the fourth dose level (DL4: 2.4 mg QD on Days 1-5) in accordance with study dose escalation schemes shown in Figure 2 based on SRC recommendation after review of the data from the initial three dose levels using the Gen 1 CC-90009 formulation.

In any cohort of 1, 3 or 6 subjects during dose escalation, all subjects are observed for at least 28 days and up to 42 days (Cycle 1, DLT window) before the next higher dose cohort can begin enrollment based on SRC review and recommendation. No more than one subject per day will be enrolled in a given dose escalation cohort. Refer to Section 7.2 for detailed information on the dose escalation process.

Dose escalation decisions will be made at the discretion of a SRC that will include Investigators (and/or designated representatives), the Sponsor's study physician, safety physician, and the study manager. Ad hoc attendees may include the study pharmacokineticist, study statistician, and additional study clinical scientists. Other internal and external experts may be consulted by the SRC, as necessary.

The SRC may decide to evaluate a higher dose cohort, additional subjects within a dose cohort, intermediate dose cohorts, smaller dose increments, alternate dosing schedules (eg, increasing from 5 to up to 10 consecutive days of CC-90009 administration), and/or declare an MTD based

on their review of available clinical and laboratory safety data, PK profiles, and PD findings. In the event that an alternate dosing schedule is evaluated, the starting dose and schedule will not exceed the dose intensity of a dose cohort that has previously met the criteria for dose escalation. An additional schedule of CC-90009 administered once daily on Days 1-3 and Days 8-10 of each 28-day schedule may be explored (Figure 3).

Protocol amendment 5 instated the use of concurrent steroid (dexamethasone or equivalent) to mitigate the risk of hypotension in all cohorts with a daily dose of 3.6 mg or higher. The rationale for dexamethasone treatment to reduce the risk of hypotension is based on pre-clinical data and clinical observations. The NTD of 3.6 mg on Days 1-5 schedule, which was determined based on DLT of hypotension, will be reevaluated for tolerability with dexamethasone (or equivalent) prophylaxis as a new cohort. Initially 3 subjects will enroll at CC-90009 3.6 mg Days 1-5 with dexamethasone (see Sections 7.2 and 8.3). If tolerated (eg, 0/3 or 1/6 DLTs), then a new NTD and MTD will be established on this schedule with concurrent dexamethasone as described above for all cohorts (Section 7, and Sections 7.2.2 – 7.2.5). Protocol amendment 7 extended the recommendation for dexamethasone to the 3.0 mg Days 1-10 schedule (see Sections 7.2 and 8.3).

Part B-Cohort Expansion

Following completion of dose escalation (Part A), one or more dosing regimens may be selected for dose expansion with up to approximately 20 evaluable subjects in each disease indication (R/R AML and R/R HR-MDS) at a specified dose level. Subjects with HR-MDS will be enrolled only during Part B (Figure 4).

In Part B, subjects with R/R AML who are eligible include subjects who relapsed after allogeneic HSCT, who are in second or later relapse, who are refractory to initial induction or re-induction treatment, who are refractory to or relapsed after hypomethylating agents (HMA failure defined as primary progression or lack of clinical benefit after a minimum of 6 cycles or unable to tolerate HMA due to toxicity), or who relapsed within 1 year of initial treatment (excluding those with favorable-risk status; see Appendix H).

In Part B, subjects with R/R HR-MDS who are eligible include subjects who scored > 3.5 points in the Revised International Prognostic Scoring System (IPSS-R) [eg, IPSS-R intermediate risk (in combination with more than 10% bone marrow blasts or poor or very poor IPSS-R cytogenetic risk), IPSS-R high and IPSS-R very high risk] and are not suitable for other established therapies (eg, transplant or hypomethylating agent) (Appendix G).

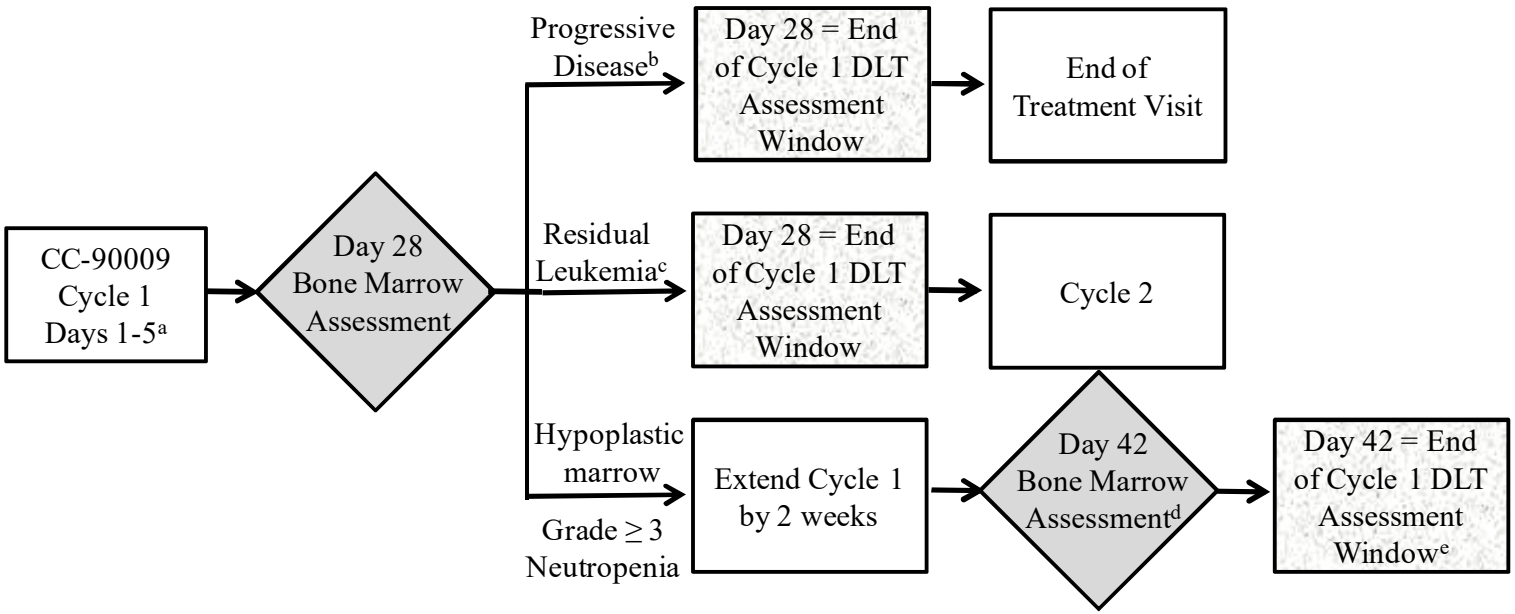
Note that the 3.6 mg dose of CC-90009 on Days 1-5 schedule with dexamethasone premedication had been selected as the Part B dose and schedule in both R/R AML and R/R HR-MDS for the dose expansion part of the study (Part B). Due to a high rate of sepsis (75%) observed in the initial 8 R/R AML subjects enrolled in Part B at dose level 3.6 mg Days 1-5 with dexamethasone premedication, the SRC recommended to close R/R AML and R/R HR-MDS cohorts receiving CC-90009 at 3.6 mg Days 1-5 for enrollment.

New cohorts in Part B will be enrolled at CC-90009 dose levels of 2.4 mg Days 1-7 and 3.0 mg Days 1-7. The selection of these doses at the Days 1-7 schedule is based primarily on PK and PD analysis and safety and tolerability data. These R/R AML and R/R HR-MDS subjects will be

pooled in each cohort by dose level for analysis of safety, PK, and PD, which will include between 6 and 40 subjects with up to 20 subjects with R/R AML and up to 20 subjects with R/R HR-MDS in each cohort. The cohorts will enroll subjects in parallel. Up to 6 subjects per cohort will be initially enrolled as a safety run-in. The SRC will assess tolerability of the dose and schedule for these initial subjects that completed at least one cycle of study treatment based on the Part A stopping criteria (Section 7.2.8) and recommend further expansion of one or more cohorts. The expanded cohort(s) will be monitored for the excess toxicities including sepsis utilizing the non-binding Bayesian stopping criterion on a continuous basis (Section 9.9.3). The SRC will continue to review safety and preliminary efficacy data regularly throughout the study and make recommendations about study continuation, cohort continuation, and dose modification, as appropriate.

The study will be conducted in compliance with International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

Figure 1: Study Schema for Dose-Limiting Toxicity Window in Part A (Dose Escalation)



DLT = dose-limiting toxicity.

[a] Modified dosing schedules (eg, increasing from 5 to 10 days) may be evaluated in additional cohorts, if necessary, based on the review by the Safety Review Committee of available safety and laboratory data, PK profiles, and PD findings.

[b] Progressive disease is defined in Section 6.4.

[c] In the absence of progressive disease (or relapse) or unacceptable toxicity, subjects may continue treatment with CC-90009 through Cycle 4 if they are deriving benefit, as judged by the Investigator (refer to Section 6.4). Additional cycles of treatment beyond Cycle 4 may be allowed after discussion with the Medical Monitor if the subject is demonstrating clinical benefit (stable disease or PR) and tolerating the study drug without unacceptable toxicity.

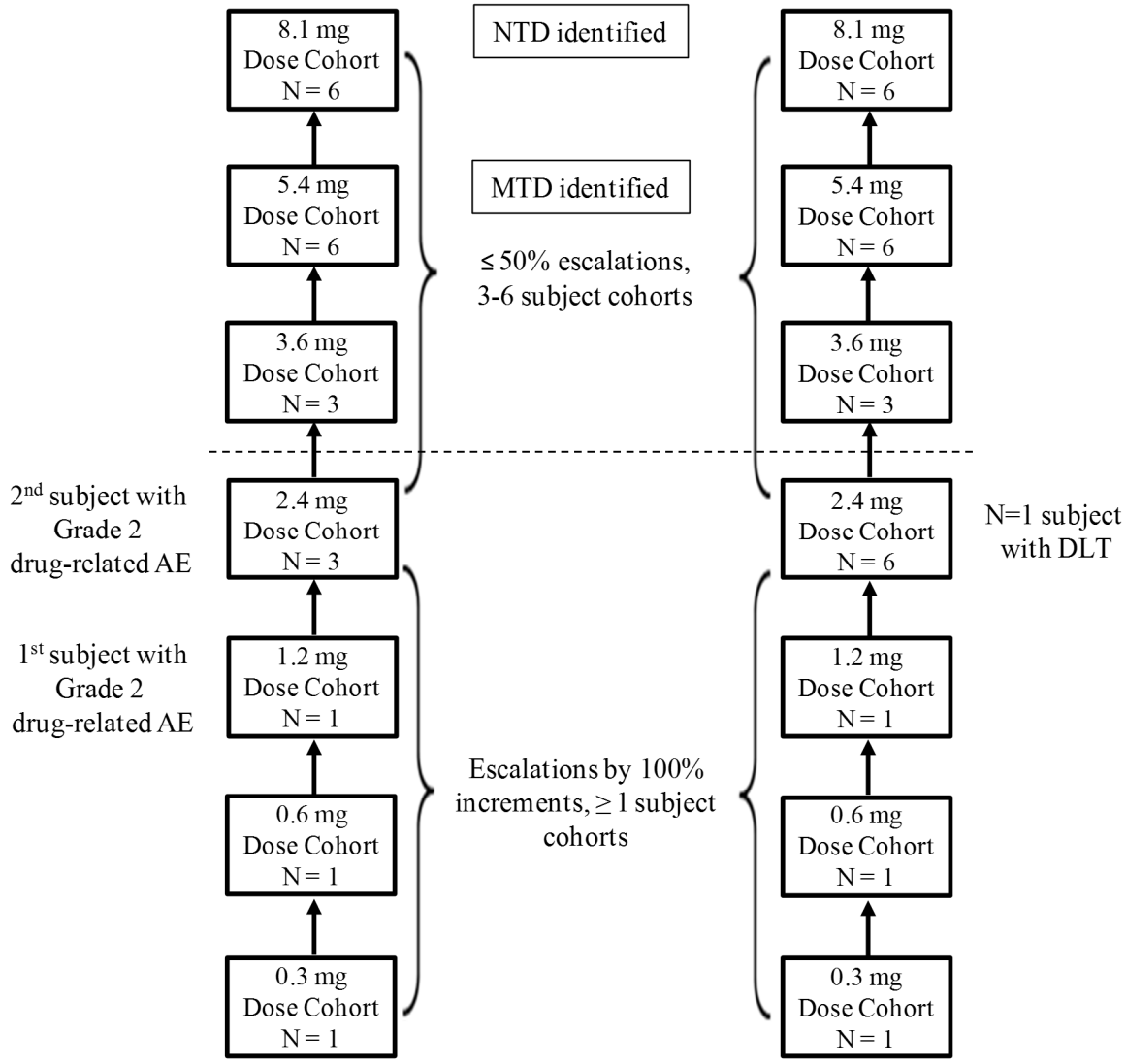
[d] Additional bone marrow assessment performed at the time of hematologic recovery or Day 42 (refer to Table 4, Table 31, Table 33, or Table 37).

[e] Eligible subjects proceed to Cycle 2.

Figure 2: Sample Dose Escalation Schemes for Part A with an NTD of 8.1 mg

Example 1

Example 2

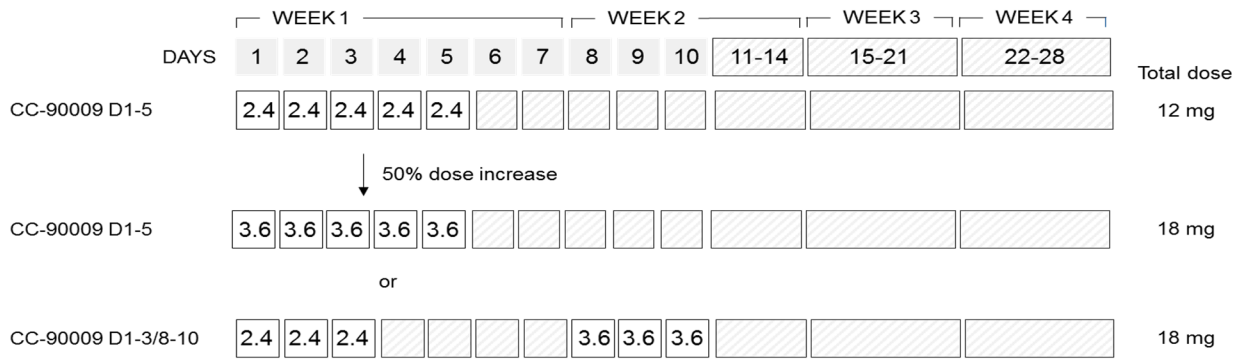


Escalations proceed by 100% increments with ≥ 1 subject cohorts until:
- ≥ 2 subjects experience a CC-90009-related Grade ≥ 2 AE in the DLT window, or
- ≥ 1 subject experiences a DLT within the DLT window

AE = adverse event; DLT = dose-limiting toxicity; MTD = maximum tolerated dose; NTD = non-tolerated dose.

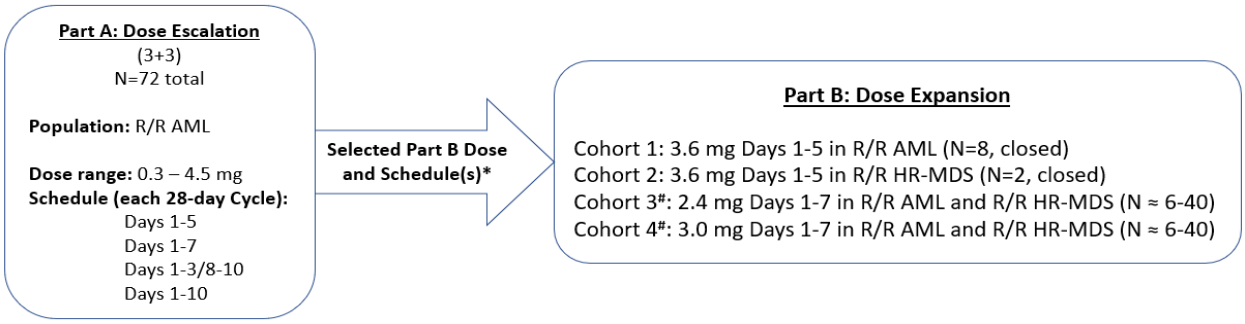
* The DMA residual solvent in the Gen 1 CC-90009 formulation must not exceed the ICH permitted daily exposure limit in order to proceed with dose escalation above a daily dose of 2.4 mg. Gen 2b CC-90009 formulation is permitted at dose levels up to 20 mg.

Figure 3: Sample Dose Escalation with or without a Schedule Change



Daily doses of CC-90009 are listing per mg as examples only. Actual selected dose/schedules require SRC approval. A 50% increase in total dose from the 3.0 mg dose level on the D1-5 schedule, total dose 15 mg, would be a 22.5 mg total dose, or a maximum of 3.2 mg per day on a D1-7 schedule, or 2.2 mg per day on a D1-10 schedule.

Figure 4: High Level Study Design



AML = acute myeloid leukemia; HR = higher-risk; MDS = myelodysplastic syndrome; N = number; R/R = relapsed or refractory

* A non-binding Bayesian stopping criterion will be utilized to monitor the excess adverse events including sepsis during Part B Dose Expansion. The SRC will continue to review safety and preliminary efficacy data regularly throughout the study and make recommendations about study continuation and dose modification, as appropriate (Section 3.1, Part B-Cohort Expansion).

Up to 20 evaluable subjects with R/R AML and up to 20 evaluable subjects with R/R HR-MDS may be enrolled in each cohort. Each cohort will enroll up to 40 evaluable subjects.

3.2 Study Duration for Subjects

Enrollment is expected to take approximately 62 to 68 months to complete (50 months for dose escalation, and approximately 12 to 18 months for expansion). Completion of active treatment and post-treatment follow-up is expected to take an additional 6 to 24 months. The entire study is expected to last up to approximately 6 to 8 years.

3.3 End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

4 STUDY POPULATION

4.1 Number of Subjects

This is a multicenter, open-label study in which approximately 72 subjects were enrolled during Part A (dose escalation) and 10 subjects were enrolled in Part B (3.6 mg Days 1-5 of 28-day schedule). During the Part B (dose expansion), up to approximately 20 evaluable subjects in each disease indication (R/R AML and R/R HR-MDS) may be enrolled in each of the planned dose expansion cohorts (2.4 mg and 3.0 mg Days 1–7 of 28-day schedules). Enrollment occurred at 12 sites in North America and/or Europe for Part A. Enrollment in Part B may include additional sites in North America and Europe. Sites that do not screen subjects may be replaced.

During Part A, no more than one subject will be enrolled per day in each dose escalation cohort.

4.2 Inclusion Criteria

Subjects must satisfy the criteria below to be enrolled in dose escalation (Part A) or dose expansion (Part B) of this study.

1) Men and women ≥ 18 years of age, at the time of signing the ICD.
2) Subject must understand and voluntarily sign an ICD prior to any study-related assessments/procedures being conducted.
3) Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4) Relapsed or refractory AML (Parts A and B) or R/R HR-MDS (Part B only) as defined by World Health Organization (WHO) criteria who are not suitable for other established therapies.
   a) In Part A, R/R AML
   b) In Part B, R/R AML including
      - Relapsed after allogeneic HSCT or
      - In second or later relapse or
      - Refractory to initial induction or re-induction treatment or
      - Refractory or relapse after HMA treatment (HMA failure defined as primary progression or lack of clinical benefit after a minimum of 6 cycles or unable to tolerate HMA due to toxicity) or
      - Relapsed within 1 year of initial treatment (excluding those with favorable risk based on cytogenetics)
   c) In Part B, R/R HR-MDS (IPSS-R > 3.5 points, IPSS-R calculated during screening period):
      - IPSS-R intermediate risk (in combination with more than 10% bone marrow blasts or poor or very poor IPSS-R cytogenetic risk) or
      - IPSS-R high or
      - IPSS-R very high risk
5) Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2.
6) At least 4 weeks (from first dose) has elapsed from donor lymphocyte infusion (DLI) without conditioning.
7) Subjects must have the following screening laboratory values:

- Corrected serum Ca or free (ionized) serum Ca within normal limits (WNL).
  - Corrected Ca (mg/dL) = Total Ca (mg/dL) – 0.8 (albumin [g/dL] – 4)
- Total White Blood Cell count (WBC) < 25 x 10^9/L prior to first infusion. Prior or concurrent treatment with hydroxyurea to achieve this level is allowed.
- Potassium and magnesium within normal limits or correctable with supplements.
- Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) or alanine aminotransferase/serum glutamate pyruvic transaminase (ALT/SGPT) ≤ 2.5 x Upper Limit of Normal (ULN).
- Uric acid ≤ 7.5 mg/dL (446 µmol/L). Prior and/or concurrent treatment with hypouricemic agents (eg, allopurinol, rasburicase) are allowed.
- Serum bilirubin ≤ 1.5 x ULN.
- Estimated serum creatinine clearance of ≥ 60 mL/min using the Cockcroft-Gault equation. Measured creatinine clearance from a 24-hour urine collection is acceptable if clinically indicated.
- INR < 1.5 x ULN and PTT < 1.5 x ULN.

8) Per the CC-90009 Pregnancy Prevention Plan (PPP) (refer to Appendix L):
   - Females of childbearing potential (FCBP; refer to Section 6.2.7) must undergo pregnancy testing based on the frequency outlined in PPP and pregnancy results must be negative.
   - Unless practicing complete abstinence from heterosexual intercourse, sexually active FCBP must agree to use adequate contraceptive methods as specified in PPP.
     - FCBP must agree to use two reliable forms of contraception simultaneously (or to practice complete abstinence), without interruption, for 28 days before starting CC-90009, throughout the entire duration of CC-90009 treatment, during dose interruptions and for at least 28 days after the last dose of CC-90009.
     - Complete abstinence is only acceptable in cases where this is the preferred and usual lifestyle of the subject.
     - Periodic abstinence (calendar ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable.
   - Unless practicing complete abstinence from heterosexual intercourse, sexually active males (including those who have had a vasectomy) must use barrier contraception (condoms) when engaging in sexual activity with FCBP as specified in PPP.
     - Complete abstinence is only acceptable in cases where this is the preferred and usual lifestyle of the subject.
     - Male patients must inform their partners who are females of childbearing potential to use two methods of reliable contraception throughout the entire duration of treatment, during dose interruptions and for at least 28 days after the last dose of CC-90009, as specified in PPP.
   - Females must agree to abstain from breastfeeding or providing breast milk for the duration specified in the PPP.
   - Males must agree not to donate semen or sperm while receiving CC-90009, during dose interruptions or for at least 28 days following the last dose of CC-90009, as specified in the PPP.

- All subjects must:
  - Understand that CC-90009 could have a potential teratogenic risk.
  - Agree to abstain from donating blood for the duration specified in the PPP.
  - Be counseled about pregnancy precautions and risks of fetal exposure (refer to PPP, Appendix L).

4.3 Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1) Subjects with acute promyelocytic leukemia (APL)
2) Subjects with clinical symptoms suggesting active central nervous system (CNS) leukemia or known CNS leukemia. Evaluation of cerebrospinal fluid is only required if there is clinical suspicion of CNS involvement by leukemia during screening.
3) Subjects with immediately life-threatening, severe complications of leukemia such as disseminated/uncontrolled infection, uncontrolled bleeding, and/or uncontrolled disseminated intravascular coagulation.
4) Disorders or conditions disrupting normal calcium homeostasis or preventing calcium supplementation including:
   - Any known condition disrupting calcium absorption.
   - Clinical evidence of hypo- or hyperparathyroidism.
   - Bisphosphonate or denosumab therapy within last 4 weeks prior to starting CC-90009.
   - Active or recent kidney stones (≤ 1 year prior to starting CC-90009).
   - Serum 25-hydroxyvitamin D level < 12 ng/mL (30 nmol/L).
5) Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
   - Left ventricular ejection fraction (LVEF) < 45% as determined by multiple gated acquisition (MUGA) scan or echocardiogram (ECHO).
   - Complete left bundle branch or bifascicular block.
   - Congenital long QT syndrome.
   - Persistent or clinically meaningful ventricular arrhythmias.
   - QTcF ≥ 470 msec on Screening electrocardiogram (ECG) (mean of triplicate recordings performed ≥ 72 hours prior to Day 1).
   - Unstable angina pectoris or myocardial infarction ≤ 3 months prior to starting CC-90009.
6) Patients with prior autologous hematopoietic stem cell transplant who, in the investigator's judgment, have not fully recovered from the effects of the last transplant (eg, transplant related side effects).
7) Prior allogeneic hematopoietic stem cell transplant (HSCT) with either standard or reduced intensity conditioning ≤ 6 months prior to starting CC-90009.
8) Subjects on systemic immunosuppressive therapy post HSCT at the time of screening, or with clinically significant graft-versus-host disease (GVHD). The use of topical steroids for ongoing skin or ocular GVHD is permitted.

9) Prior systemic cancer-directed treatments or investigational modalities ≤ 5 half-lives or 4 weeks prior to starting CC-90009, whichever is shorter. Hydroxyurea is allowed to control peripheral leukemia blasts.
10) Leukapheresis ≤ 2 weeks prior to starting CC-90009.
11) Major surgery ≤ 2 weeks prior to starting CC-90009. Subjects must have recovered from any clinically significant effects of recent surgery.
12) Pregnant or nursing females.
13) Known human immunodeficiency virus (HIV) infection.
14) Known chronic, active hepatitis B or C (HBV/HCV) infection.
15) Ongoing treatment with chronic, therapeutic dosing of anti-coagulants (eg, warfarin, low molecular weight heparin, Factor Xa inhibitors).
16) History of concurrent second cancers requiring active, ongoing systemic treatment.
17) Subject has a known allergy/hypersensitivity to calcium, calcitriol, and/or vitamin D supplements or any of their ingredients.
18) Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
19) Subject has any condition, including active or uncontrolled infection, or the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
20) Subject has any condition that confounds the ability to interpret data from the study.
21) Disorders or conditions that would, in the investigator's judgment, prevent the subject from receiving concomitant corticosteroids (only for dose levels of CC-90009 at or above 3.6 mg).
22) For Part B, previous SARS-CoV-2 infection within 10 days for mild or asymptomatic infections or 20 days for severe/critical illness prior to C1D1. Acute symptoms must have resolved and based on investigator assessment in consultation with the Sponsor Medical Monitor, there are no sequelae that would place the subject at a higher risk of receiving study treatment.
23) For Part B, previous COVID-19 vaccine within 14 days of C1D1. For vaccines requiring more than one dose, the full series (eg, both doses of a two-dose series) should be completed at least 14 days prior to C1D1 when feasible and when a delay in C1D1 would not put the study subject at risk.

5 TABLE OF EVENTS

For a detailed description of the procedures listed, please refer to Section 6. For details regarding CC-90009 administration, please refer to Section 7. Procedures for Part A Cycle 1 are shown in Table 4 and Part A Cycles 2 and higher are shown in Table 5. Based on the Day 28 bone marrow evaluation, subjects with hypoplastic bone marrow without evidence of persistent leukemia who have Grade ≥ 3 neutropenia will be followed for an additional 2 weeks for safety monitoring in Cycle 1 (total duration of 42 days; refer to Figure 1).

Table 4: Table of Events for Cycle 1 in Part A (D1-5 Schedule)

		Treatment Period												
		Cycle 1												
	Screening	WK1							WK2	WK3	WK4		WK5[b]	WK6[b]
Events[a]	**D-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D15**	**D22**	**D28[c]**	**D29**	**D36**
Study Entry (Section 6.1)														
Informed consent	X													
Inclusion/ exclusion criteria	X													
Medical/ oncologic history	X													
Demographics	X													
IRT registration	X	X												
Pregnancy risk counseling and contraceptive compliance confirmation	X	As specified in Section 6.1.1 and the PPP in Appendix L												
Prior/ concomitant medications & procedures (Section 6.2.1)	X	X	X	X	X	X	X	X	X	X	X		X	X
CC-90009 Administration (Section 7)														
Calcium, calcitriol, and vitamin D supplements and recording on diary card (refer to Section 7.2)	X (D-3 to D-1)	X	X	X	X	X	X	X	X[d]			X[d]		X[d]
Provide/ review diary card	X	X												
Corticosteroid administration (dexamethasone) (refer to Section 7.2) for doses 3.6 mg and above		X	X	X	X	X								
IV administration of CC-90009[e]		X	X	X	X	X								

Table 4: Table of Events for Cycle 1 in Part A (D1-5 Schedule)

		Treatment Period												
		Cycle 1												
	Screening	WK1							WK2	WK3	WK4		WK5[b]	WK6[b]
Events[a]	D-28 to -1	D1	D2	D3	D4	D5	D6	D7	D8	D15	D22	D28[c]	D29	D36
Monitoring as inpatient		X	X	X	X	X								
Safety Assessments (Section 6)														
Adverse Event Evaluation (Section 6.2.2)	X	X	X	X	X	X	X	X	X	X	X		X	X
Height	X													
Weight (Section 6.2.3)	X	X							X	X	X			
Vital Signs (Section 6.2.3)	X	X[f]	X[f]	X[f]	X[f]	X[f]	X	X	X	X	X		X	X
Physical Examination (Section 6.2.4)	X	X							X					
ECOG PS (Appendix D)	X	X							X					
12-lead ECG (in triplicate, Section 6.2.5)	X (≥72 hrs prior to D1)	X[f]				X[f]			X					
LVEF (ECHO/MUGA scan; Section 6.2.6)	X													
Pregnancy testing per PPP (FCBP only; Section 6.2.7)	X[g]								X	X	X			X
Hematology laboratory tests (Section 6.2.8)	X (D-14 to -1)	X	X	X	X	X	X	X	X	X	X		X	X
G6PD (Section 6.2.8)	X													
Serum chemistry laboratory tests (Section 6.2.8)[h]	X (D-3 to -1)	X[i]	X[i]	X[i]	X	X	X	X	X	X	X		X	X
Additional serum Ca, Mg and PTH tests (Section 6.2.8)[h]		X[j]	X[j]	X[j]	X[j]	X[j]								
Serum PTH, P1NP, β-CTx tests (Section 6.2.8)		X							X	X	X			

Table 4: Table of Events for Cycle 1 in Part A (D1-5 Schedule)

Events[a]		Treatment Period												
		Cycle 1												
	Screening	WK1							WK2	WK3	WK4		WK5[b]	WK6[b]
	D-28 to -1	D1	D2	D3	D4	D5	D6	D7	D8	D15	D22	D28[c]	D29	D36
Serum 25-hydroxyvitamin D level (Section 6.2.8)	X	X												
Urine Ca/ creatinine ratio (random) (Section 6.2.8)		X							X	X	X			
Amylase, lipase, T-cell subsets (CD4+ and CD8+), TSH (Section 6.2.8)		X												
PT, INR, PTT (Section 6.2.8)[k]	X													
Urinalysis (Section 6.2.8)	X (D-14 to -1)									X				
PK & PD Assessments														
Blood, PK (Section 6.5)		X[l]	X	X[l]	X	X[l]	X							
Urine, PK (Section 6.5) selected subjects[r]		X												
Pharmacogenomics sample (eg, buccal cells or nail clippings), (Section 6.6.1)		X												
Blood (whole), biomarker flow cytometry (Section 6.6.2)	X (D-14 to -1)	X[l]	X[l]	X[l]					X	X				
Blood (PBMCs), PD protein and RNA (Section 6.6.2)	X (D-14 to -1)	X[l]	X	X					X					
Blood (PBMCs), PD ex vivo sensitivity assays, phenotyping & sequencing (Section 6.6.2)		X												
Blood (plasma), PD cytokines (Section 6.6.2)	X (D-14 to -1)	X	X	X	X				X					

Table 4: Table of Events for Cycle 1 in Part A (D1-5 Schedule)

		Treatment Period												
		Cycle 1												
	Screening	WK1							WK2	WK3	WK4		WK5[b]	WK6[b]
Events[a]	D-28 to -1	D1	D2	D3	D4	D5	D6	D7	D8	D15	D22	D28[c]	D29	D36
Bone marrow aspirate and biopsy, PD biomarkers & MRD (Section 6.6.3)[m]	X (D-14 to -1)					X[n]						X (± 3d)		
Efficacy														
Bone marrow aspiration and biopsy, complete blood counts and examination of peripheral blood smears (Section 6.4)[o]	X (D-14 to -1)[p]											X (± 3d)		X (only on D42 ± 3d)[q]

Abbreviations: β-CTx = beta C-terminal telopeptide; C = cycle; Ca = calcium; CD = cluster of differentiation; D = day; ECHO = echocardiogram; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FCBP = females of child bearing potential; G6PD = glucose-6-phosphate dehydrogenase; hrs = hours; INR = international normalized ratio; IRT = integrated response technology; IV = intravenous; LVEF = left ventricular ejection fraction; Mg = magnesium; MRD = Minimal Residual Disease; MUGA = multi-gated acquisition scan; P1NP = procollagen type 1 N-terminal propeptide; PBMC = peripheral blood mononuclear cells; PD = pharmacodynamic; PK = pharmacokinetic; PPP = pregnancy prevention plan; PT = prothrombin time; PTH = parathyroid hormone; PTT = partial thromboplastin time; RNA = ribonucleic acid; TSH = thyroid-stimulating hormone; WK = week.

[a] All study visits/procedures will have a ± 2 day window and all laboratory blood samples should be drawn predose (≤ 5 hrs), unless otherwise specified in this table or Section 6.

[b] Subjects with hypoplastic bone marrow without evidence of persistent AML at the Day 28 assessment who have Grade ≥ 3 neutropenia will be followed for an additional 2 weeks for safety monitoring in Cycle 1 (total duration of 42 days; refer to Figure 1). Not all visits are shown as separate columns under Week 6, ie, Day 42 bone marrow assessment.

[c] Eligible subjects continue on to Cycle 2 (refer to Table 5). Based on the Day 28 bone marrow evaluation, subjects with a hypoplastic bone marrow without evidence of persistent leukemia who have Grade ≥ 3 neutropenia will be followed for an additional 2 weeks for safety monitoring in Cycle 1.

[d] Supplementation may be prolonged if hypocalcemia occurs (refer to Section 7.2.13.2). Subjects are to start supplements at least 3 days prior to Day 1 of Cycle 2 as per Section 7.2.

[e] Subjects will be closely monitored during administration of CC-90009 and for at least one hour after. Subjects should be adequately hydrated to prevent potential tumor lysis syndrome (TLS) (eg, 2 to 3 liters of oral or IV fluids per day) starting the day prior to CC-90009 administration and continuing through each day of CC-90009 administration. Refer to Section 7.2.12 for information on dose interruptions. The SRC may decide to evaluate alternate dosing schedules (eg, increasing from 5 to up to 10 consecutive days of CC-90009 administration) based on their review of available clinical and laboratory safety data, PK profiles, and PD findings.

[f] Multiple measurements performed on this day.

[g] Two pregnancy tests (sensitivity of at least 25 mIU/mL) must be performed prior to first dose of CC-90009: within 10 to 14 days prior and within 24 hours prior. Both tests must be negative for CC-90009 dosing to begin.

[h] A free (ionized) serum calcium test should be obtained at Screening to establish baseline values in addition to the corrected serum calcium test (corrected for albumin) used to fulfill the inclusion criteria. In the event of Grade ≥ 2 hypocalcemia or symptoms of hypocalcemia (eg, carpopedal spasm, tetany, seizures, etc), subjects must be hospitalized.

Also, if Grade ≥ 2 hypocalcemia and abnormal levels of serum albumin occurs, a serum ionized calcium test must be performed. Refer to Section 7.2.13.2 for hypocalcemia management guidelines.

[i] Specific tests for TLS monitoring required predose and 12 hours (± 1 hour) postdose on Days 1, 2, and 3. Refer to Section 6.2.8.

[j] Additional serum calcium/magnesium tests required 6 and 12 hours (± 1 hour) postdose on days of CC-90009 administration. Additional PTH tests required at 6 hours (± 1 hours) post-dose on days of CC-90009 administration.

[k] Subsequent coagulation tests only performed for subjects on anticoagulant therapy and as clinically indicated.

[l] Multiple blood samples will be collected for this assay on the specified day. Refer to Sections 6.5 and 6.6.

[m] Bone marrow samples for biomarker assessment are mandatory. If bone marrow samples are scheduled to be collected on the same day for efficacy, the biomarker samples should be collected at the same time. If sufficient bone marrow aspirate specimen is not available, peripheral blood may be submitted in place of the BMA specimen for biomarker studies (eg, MRD); see laboratory manual for details.

[n] Obtained between 4 to 8 hours postdose. The samples may be obtained on Day 4 if necessary due to scheduling difficulties.

[o] Additional aspirates and biopsies will be collected as clinically indicated (eg, Cycle 1 Day 15 based on Investigator's medical assessment).

[p] Molecular and cytogenetic studies may be omitted at: Screening, if they were completed within the previous 90 days and the results are available for recording on the electronic case report forms and Day 42 (or at hematologic recovery), if a complete response is documented at Day 28.

[q] Additional bone marrow assessment performed at the time of hematologic recovery or Day 42 (± 3 days). Eligible subjects continue on to Cycle 2 (refer to Table 5).

[r] Urine PK to be performed on approximately 10 selected subjects from Part A and/or Part B. This is a 24-hour collection that starts on C1D1 and ends on C1D2.

Table 5: Table of Events for Cycles ≥ 2 in Part A (D1-5 Schedule), End of Treatment Visit, and Follow-up Period

	Treatment Period										Follow-up Period	
	Cycles ≥ 2											
	WK1					WK2	WK3	WK4		EOT[b]	Safety[c]	
Events[a]	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 22	Day 28	≤ 28 days	28 days (± 3 days)	Long Term
Review concomitant medications & procedures (Section 6.2.1)	X	X	X	X	X	X	X	X		X	X	
CC-90009 Administration (Section 7)												
Calcium, calcitriol and Vitamin D supplements and recording on diary card (Section 7.2)	X	X	X	X	X[d]	X[d]			X (C2 and C3)[d]			
Provide/ review of diary card	X									X		
Corticosteroid administration (dexamethasone) (refer to Section 7.2) for doses 3.6 mg and above	X	X	X	X	X							
IV administration of CC-90009[e]	X	X	X	X	X							
Safety Assessments (Section 6)												
Adverse Event Evaluation (Section 6.2.2)	X	X	X	X	X	X	X	X		X	X	
Weight (Section 6.2.3)	X									X		
Vital Signs (Section 6.2.3)	X[f]	X[f]	X[f]	X[f]	X[f]	X	X	X		X		
Physical Examination (Section 6.2.4)	X									X		
ECOG PS (Appendix D)	X									X		
12-lead ECG (Section 6.2.5)[g]	X									X		
LVEF (ECHO/MUGA; Section 6.2.6)	X (only C2 ± 7d)									X (± 7d)[h]		
Pregnancy test (FCBP only; Section 6.2.7)	X						X[i]			X[i]	X[i]	
Pregnancy risk counseling and contraceptive compliance confirmation	X	As specified in Section 6.1.1 and the PPP in Appendix L										
Hematology laboratory (Section 6.2.8)	X	X	X	X	X	X	X	X		X		

Table 5: Table of Events for Cycles ≥ 2 in Part A (D1-5 Schedule), End of Treatment Visit, and Follow-up Period

	Treatment Period										Follow-up Period	
	Cycles ≥ 2											
	WK1					WK2	WK3	WK4		EOT[b]	Safety[c]	
Events[a]	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 22	Day 28	≤ 28 days	28 days (± 3 days)	Long Term
Serum chemistry laboratory tests (Section 6.2.8)[j]	X	X				X	X	X		X		
Serum Ca & Mg tests (Section 6.2.8)[j]	X[j]	X[j]	X[j]	X[j]	X[j]							
Serum PTH, P1NP, β-CTx tests (Section 6.2.8)	X				X					X		
Serum 25-hydroxyvitamin D level (Section 6.2.8)	X											
Urine Ca/ creatinine ratio test (random) (Section 6.2.8)	X				X					X		
Amylase, lipase, T-cell subsets (CD4+ and CD8+), TSH (Section 6.2.8)	X									X		
PT, INR, PTT (for subjects on anticoagulant therapy) (Section 6.2.8)	X									X		
Urinalysis (Section 6.2.8)	X									X		
PK & PD Assessments												
Blood, PK (Section 6.5)[o]	X	X	X	X	X[o]							
Blood (whole), biomarker flow cytometry, (Section 6.6.2) first cycle of intra-subject dose escalation only[k]	X[k]	X[k]	X[k]			X[k]	X[k]					
Blood (PBMCs), PD protein and RNA (Section 6.6.2) first cycle of intra-subject dose escalation only[k]	X[k]	X[k]	X[k]			X[k]						
Blood (plasma), PD cytokines (Section 6.6.2) first cycle of intra-subject dose escalation only[k]	X	X	X	X		X						

Table 5: Table of Events for Cycles ≥ 2 in Part A (D1-5 Schedule), End of Treatment Visit, and Follow-up Period

	Treatment Period										Follow-up Period	
	Cycles ≥ 2											
	WK1					WK2	WK3	WK4		EOT[b]	Safety[c]	
Events[a]	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**≤ 28 days**	**28 days (± 3 days)**	**Long Term**
Bone marrow aspirate and biopsy, PD biomarkers & MRD (Section 6.6.3)[l, m]									X (C2 and C4; ± 3d)	X[n]		Refer to Section 6.3.2
Efficacy												
Complete blood counts and examination of peripheral blood smears (Section 6.4)[m]									X (C2 and C4; ± 3d)	X[n]		Refer to Section 6.3.2
Bone marrow aspirate and biopsy (Section 6.4)[m]									X (C2 and C4; ± 3d)	X[n]		Refer to Section 6.3.2
Follow-up												
CC-90009-related AE/SAE follow-up	Refer to Section 6.3.1											
Anticancer therapies	Refer to Section 6.3.2											
Survival	Refer to Section 6.3.3											

Abbreviations: Adverse event = AE; β-CTx = beta C-terminal telopeptide; C = cycle; Ca = calcium; CD = cluster of differentiation; D = day; ECHO = echocardiogram; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; FCBP = females of child bearing potential; INR = international normalized ratio; IV = intravenous; LVEF = left ventricular ejection fraction; Mg = magnesium; MUGA = multi-gated acquisition scan; P1NP = procollagen type 1 N-terminal propeptide; PD = pharmacodynamics; PPP = pregnancy prevention plan; PT = prothrombin time; PTH = parathyroid hormone; PTT = partial thromboplastin time; q = every; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WK = week.

[a] All study visits/procedures will have a ± 2 day window and all laboratory blood samples should be drawn predose (≤ 5 hrs), unless otherwise specified in this table or Section 6. Cycles should start ≤ 7 days after the last day of the previous cycle.

[b] EOT Visit performed within 28 days after last dose of CC-90009 for subjects that discontinue prior to completing dosing in Cycle 4. For subjects that complete dosing in Cycle 4, this visit should be completed on Day 28 (± 2 days) of Cycle 4. For subjects who complete dosing after Cycle 4, EOT Visit should be completed within 28 days after the last day of the previous cycle.

[c] Safety Follow-up Visit is performed 28 days (± 3 days) after the last dose of CC-90009 for all subjects. May be performed by telephone contact if pregnancy testing is not required (refer to footnote "i").

[d] Supplements to be administered for at least 3 days after the last dose in each cycle. Supplementation may be prolonged if hypocalcemia occurs (refer to Section 7.2.13.2). Subjects to start supplements at least 3 days prior to Day 1 of Cycles 3 and 4 as per Section 7.2.

[e] Subjects will be closely monitored during the administration of CC-90009 and for at least 1 hour after. Subjects should be adequately hydrated to prevent potential tumor lysis syndrome (TLS) (eg, 2 to 3 liters of oral or IV fluids per day) starting the day prior to CC-90009 administration and continuing through each day of CC-90009 administration. Refer to Section 7.2.12 for information on dose interruptions. The SRC may decide to evaluate alternate dosing schedules (eg, increasing from 5 to up to 10 consecutive days of CC-90009 administration) based on their review of available clinical and laboratory safety data, PK profiles, and PD findings. Subjects should be administered Cycle ≥ 2 of CC-90009 in a Limited Stay Unit (LSU) or as inpatient. Subjects experiencing Grade ≥ 2 hypocalcemia during any cycle should be administered CC-90009 in the inpatient setting for subsequent cycles (an exception can be made for subjects with grade 2 hypocalcemia lasting less than 24 hours that recovers without IV calcium [eg, calcium gluconate or calcium chloride] after discussion with the Celgene medical monitor).

[f] Multiple measurements performed on this day.

[g] Triplicate ECGs will be performed on Day 1 of each cycle (refer to Section 6.2.5) and a single ECG obtained at the EOT visit.

[h] The EOT Visit LVEF is not required if the prior LVEF was performed within 56 days.

[i] Per the PPP, a pregnancy test is required 28 days after the last dose of for all FCBP. For FCBP with irregular menstrual periods, a pregnancy test is required every 14 days (ie, Day 15 of Cycles ≥ 2 and at 14 and 28 days after the last dose of CC-90009).

[j] In the event of Grade ≥ 2 hypocalcemia or symptoms of hypocalcemia (eg, carpopedal spasm, tetany, seizures, etc), subjects must be hospitalized. Also, if Grade ≥ 2 hypocalcemia and abnormal levels of serum albumin occurs, a serum ionized calcium test must be performed. Refer to Section 7.2.13.2 for hypocalcemia management guidelines. Refer to Section 6.2.8 for required days and timing of tests. Subjects who experienced Grade ≥ 2 hypocalcemia during Cycle 1, require testing Days 1-5 at 6 and 12 hours postdose. All other subjects require testing prior to dosing. If intra-subject dose escalation occurs, subjects should be treated as in Cycle 1.

[k] If intra-subject dose escalation occurs, blood samples for PD assays will be collected during the first cycle only at the increased dose; see laboratory manual for details. Multiple blood samples will be collected for this assay on the specified Days 1, 2, 3. Refer to Section 6.6.

[l] Bone marrow samples for biomarker PD assessment are mandatory. When applicable (refer to time points in the table above), bone marrow samples for biomarker PD assessment will be obtained at the same time as a scheduled efficacy assessment. If sufficient bone marrow aspirate specimen is not available, peripheral blood may be submitted in place of the BMA specimen for biomarker studies (eg, MRD); see laboratory manual for details.

[m] If end of Cycle 2 (Day 28 ± 3 days) samples are obtained on Day 1 of Cycle 3, they must be obtained prior to CC-90009 administration. Additionally, bone marrow aspirates and biopsies may be obtained in both Part A and Part B, after a CR is confirmed, if relapse is suspected, or following treatment discontinuation to elucidate effects of long-term treatment or resistance mechanisms. Additional aspirates and biopsies will be collected as clinically indicated based on the Investigator's medical assessment.

[n] For subjects that complete dosing in Cycle 4, performed/obtained once on Day 28 (± 3 days). For subjects that continue (after consultation with Medical Monitor) beyond Cycle 4, efficacy and bone marrow PD assessments may be obtained to confirm a CR, if relapse is suspected, or following treatment discontinuation to elucidate effects of long-term treatment or resistance mechanisms. Additional aspirates and biopsies will be collected as clinically indicated based on the Investigator's medical assessment. Refer to Section 6.3.2 and Section 6.4.

[o] Blood samples for PK are to be collected in Cycle 2 only; on Day 5 there is a pre-dose and 24 hour postdose sample Section 6.5.1.

Tables of Events for the alternate dosing schedules (eg, D1-3/D8-10 Dosing Schedules, D1-7 Dosing Schedule, and D1-10 Dosing Schedule) are located in Appendix K and Appendices M-O. All new dose levels (including dosing schedule changes) require prior approval from the SRC before use (Section 3.1). Procedures for Part B (D1-5 Schedule) Cycle 1 are shown in Table 6 and Part B (D1-5 Schedule) Cycles 2 and higher are shown in Table 7.

Table 6: Table of Events for Cycle 1 in Part B (D1-5 Schedule)

		Treatment Period										
		Cycle 1										
	Screening	WK1							WK2	WK3	WK4	
Events[a]	**D-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D15**	**D22**	**D28**[c]
Study Entry (Section 6.1)												
Informed consent	X											
Inclusion/ exclusion criteria	X											
Medical[t]/ oncologic history	X											
AML or MDS Disease Assessment and Cohort Assignment[b]	X											
Demographics	X											
IRT registration	X	X										
Pregnancy risk counseling and contraceptive compliance confirmation	X	As specified in Section 6.1.1 and the PPP in Appendix L										
Prior/ concomitant medications & procedures (Section 6.2.1)	X	X	X	X	X	X	X	X	X	X	X	
CC-90009 Administration (Section 7)												
Calcium, calcitriol, and vitamin D supplements and recording on diary card (refer to Section 7.2)	X (D-3 to D-1)	X	X	X	X	X	X	X	X[d]			
Provide/review diary card	X	X										
Corticosteroid administration (dexamethasone) (refer to Section 7.2) for doses 3.6 mg and above		X	X	X	X	X						
IV administration of CC-90009		X	X	X	X	X						
Monitoring as an inpatient		X	X	X	X	X						
Safety Assessments (Section 6)												
Adverse Event Evaluation (Section 6.2.2)	X	X	X	X	X	X	X	X	X	X	X	

Table 6: Table of Events for Cycle 1 in Part B (D1-5 Schedule)

		Treatment Period										
		Cycle 1										
	Screening	WK1							WK2	WK3	WK4	
Events[a]	D-28 to -1	D1	D2	D3	D4	D5	D6	D7	D8	D15	D22	D28[c]
Height	X											
Weight (Section 6.2.3)	X	X							X	X	X	
Vital Signs (Section 6.2.3)	X	X[f]	X[f]	X[f]	X[f]	X[f]	X	X	X	X	X	
Physical Examination (Section 6.2.4)	X	X							X			
ECOG PS (Appendix D)	X	X							X			
SARS-CoV-2 Viral Testing[r]	X (within 7 days of D1)											
12-lead ECG (in triplicate, Section 6.2.5)	X (≥72 hrs prior to D1)	X[f]				X[f]			X			
LVEF (ECHO/MUGA scan; Section 6.2.6)	X											
Pregnancy testing per PPP (FCBP only; Section 6.2.7)	X[g]								X	X	X	
Hematology laboratory tests (Section 6.2.8)	X (D-14 to -1)	X	X	X	X	X	X	X	X	X	X	
G6PD (Section 6.2.8)	X											
Serum chemistry laboratory tests (Section 6.2.8)[h]	X (D-3 to -1)	X[i]	X[i]	X[i]	X	X			X	X	X	
Additional serum Ca, Mg and PTH tests (Section 6.2.8)[h]		X[j]	X[j]	X[j]	X[j]	X[j]						
Serum 25-hydroxyvitamin D level (Section 6.2.8)	X	X										

Table 6: Table of Events for Cycle 1 in Part B (D1-5 Schedule)

		Treatment Period										
		Cycle 1										
	Screening	WK1							WK2	WK3	WK4	
Events[a]	**D-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D15**	**D22**	**D28**[c]
Serum PTH test Urine Ca/ creatinine ratio (random) (Section 6.2.8)		X							X	X	X	
Serum P1NP and β-CTx tests (Section 6.2.8)		X								X		
Amylase, lipase, T-cell subsets (CD4+ and CD8+), TSH (Section 6.2.8)		X										
PT, INR, PTT (Section 6.2.8)[k]	X											
Urinalysis (Section 6.2.8)	X (D-14 to -1)									X		
PK & PD Assessments												
Blood, PK (Section 6.5)		X[l]	X									
Urine, PK (Section 6.5) selected subjects[q]		X										
Pharmacogenomics sample (eg, buccal cells or nail clippings), (Section 6.6.1)		X										
SARS-CoV-2 serology[s] (Section 6.6.4)		X										
Blood (whole), biomarker flow cytometry (Section 6.6.2)	X (D-14 to -1)	X[l]		X[l]					X			X
Blood (whole), PD biomarker (Section 6.6.2)	X (D-14 to -1)					X[n]						X (± 3d)
Blood (PBMCs), PD protein and RNA (Section 6.6.2)	X (D-14 to -1)	X		X					X			
Blood (PBMCs), PD ex vivo sensitivity assays, phenotyping & sequencing (Section 6.6.2)		X										

Table 6: Table of Events for Cycle 1 in Part B (D1-5 Schedule)

		Treatment Period										
		Cycle 1										
	Screening	WK1							WK2	WK3	WK4	
Events[a]	D-28 to -1	D1	D2	D3	D4	D5	D6	D7	D8	D15	D22	D28[c]
Blood (plasma), PD cytokines (Section 6.6.2)	X (D-14 to -1)	X	X	X	X				X			
Bone marrow aspirate and biopsy, PD biomarkers & MRD (Section 6.6.3)[m]	X (D-14 to -1)					X[n]						X (± 3d)
Bone marrow aspiration and biopsy, complete blood counts and examination of peripheral blood smears (Section 6.4)[o]	X (D-14 to -1)[p]											X (± 3d)

Abbreviations: β-CTx = beta C-terminal telopeptide; C = cycle; Ca = calcium; CD = cluster of differentiation; D = day; ECHO = echocardiogram; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FCBP = females of child bearing potential; G6PD = glucose-6-phosphate dehydrogenase; hrs = hours; INR = international normalized ratio; IRT = integrated response technology; IV = intravenous; LVEF = left ventricular ejection fraction; Mg = magnesium; MRD = Minimal Residual Disease; MUGA = multi-gated acquisition scan; P1NP = procollagen type 1 N-terminal propeptide; PBMC = peripheral blood mononuclear cells; PD = pharmacodynamics; PK = pharmacokinetic; PPP = pregnancy prevention plan; PT = prothrombin time; PTH = parathyroid hormone; PTT = partial thromboplastin time; RNA = ribonucleic acid; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; TSH = thyroid-stimulating hormone; WK = week.

[a] All study visits/procedures will have a ± 2 day window and all laboratory blood samples should be drawn predose (≤ 5 hrs), unless otherwise specified in this table or Section 6.

[b] See Section 6.1 for details regarding collecting BMA/BMB, PBS, and cytogenetics at screening for assessing AML/MDS diagnosis, for potential retrospective confirmation of mutational status, and collecting BMA and PB at screening for pharmacodynamics and correlative studies. A bone marrow biopsy can be collected in conjunction with an aspirate if it is standard institutional practice. A bone marrow biopsy must be collected if adequate aspirate sample is not attainable.

[c] Eligible subjects continue on to Cycle 2 (refer to Table 7).

[d] Supplementation may be prolonged if hypocalcemia occurs (refer to Section 7.2.13.2). Subjects are to start supplements at least 3 days prior to Day 1 of Cycle 2 as per Section 7.2.

[e] Subjects will be closely monitored during administration of CC-90009 and for at least one hour after. Subjects should be adequately hydrated to prevent potential tumor lysis syndrome (TLS) (eg, 2 to 3 liters of oral or IV fluids per day) starting the day prior to CC-90009 administration and continuing through each day of CC-90009 administration. Refer to Section 7.2.12 for information on dose interruptions. The SRC may decide to evaluate alternate dosing schedules (eg, increasing from 5 to up to 10 consecutive days of CC-90009 administration) based on their review of available clinical and laboratory safety data, PK profiles, and PD findings.

[f] Multiple measurements performed on this day.

[g] Two pregnancy tests (sensitivity of at least 25 mIU/mL) must be performed prior to first dose of CC-90009: within 10 to 14 days prior and within 24 hours prior. Both tests must be negative for CC-90009 dosing to begin.

[h] A free (ionized) serum calcium test should be obtained at Screening to establish baseline values in addition to the corrected serum calcium test (corrected for albumin) used to fulfill the inclusion criteria. In the event of Grade ≥ 2 hypocalcemia or symptoms of hypocalcemia (eg, carpopedal spasm, tetany, seizures, etc), subjects must be hospitalized. Also, if Grade ≥ 2 hypocalcemia and abnormal levels of serum albumin occurs, a serum ionized calcium test must be performed. Refer to Section 7.2.13.2 for hypocalcemia management guidelines.

[i] Specific tests for TLS monitoring required predose and 12 hours (± 1 hour) postdose on Days 1, 2, and 3. Refer to Section 6.2.8.

[j] Additional serum calcium/magnesium tests required 6 and 12 hours (± 1 hour) postdose on days of CC-90009 administration. Additional PTH tests required at 6 hours (± 1 hours) post-dose on days of CC-90009 administration.

[k] Subsequent coagulation tests only performed for subjects on anticoagulant therapy and as clinically indicated.

[l] Multiple blood samples will be collected for this assay on the specified day. Refer to Sections 6.5 and 6.6.

[m] Bone marrow samples for biomarker assessment are mandatory. If bone marrow samples are scheduled to be collected on the same day for efficacy, the biomarker samples should be collected at the same time. If sufficient bone marrow aspirate specimen is not available, peripheral blood may be submitted in place of the BMA specimen for biomarker studies (eg, MRD); see laboratory manual for details.

[n] Obtained between 4 to 8 hours postdose. The samples may be obtained on Day 4 if necessary due to scheduling difficulties.

[o] Additional aspirates and biopsies will be collected as clinically indicated (eg, Cycle 1 Day 15 based on Investigator's medical assessment).

[p] Molecular and cytogenetic studies may be omitted at: Screening, if they were completed within the previous 90 days and the results are available for recording on the electronic case report forms; see Section 6.1 for details on sending samples to the central laboratory.

[q] Urine PK to be performed on approximately 10 selected subjects from Part A and/or Part B. This is a 24-hour collection that starts C1D1 and ends C1D2.

[r] RT-PCR testing for SARS-CoV-2 is mandatory within 7 days prior to first dose of CC-90009 (C1D1). The RT-PCR test should be based on institutional or local guidelines. Please see Section 6.1 in the event of a positive result.

[s] Serum will be collected at predose on Cycle 1 Day 1 (or at screening), approximately every 6 months during study treatment and at EOT to be used for possible measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG). Results will not be used to determine eligibility. Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection.

[t] Medical history will also include COVID-19 vaccines, toxicities of prior treatments, and known allergies.

Table 7: Table of Events for Cycles ≥ 2 in Part B (D1-5 Schedule), End of Treatment Visit, and Follow-up Period

	Treatment Period										Follow-up Period	
	Cycles ≥ 2											
	WK1					WK2	WK3	WK4		EOT[b]	Safety[c]	
Events[a]	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 15**	**Day 22**	**Day 28**	**≤ 28 days**	**28 days (± 3 days)**	**Long Term**
Review concomitant medications & procedures (Section 6.2.1)	X	X	X	X	X	X	X	X	X	X	X	
CC-90009 Administration (Section 7)												
Calcium, calcitriol and Vitamin D supplements and recording on diary card (Section 7.2)	X	X	X	X	X[d]	X[d]			X (C2 and C3)[d]			
Provide/ review of diary card	X									X		
Corticosteroid administration (dexamethasone) (refer to Section 7.2) for doses 3.6 mg and above	X	X	X	X	X							
IV administration of CC-90009[e]	X	X	X	X	X							
Safety Assessments (Section 6)												
Adverse Event Evaluation (Section 6.2.2)	X	X	X	X	X	X	X	X		X	X	
Weight (Section 6.2.3)	X									X		
Vital Signs (Section 6.2.3)	X[f]	X[f]	X[f]	X[f]	X[f]	X	X	X		X		
Physical Examination (Section 6.2.4)	X									X		
ECOG PS (Appendix D)	X									X		
12-lead ECG (Section 6.2.5)[g]	X									X		
LVEF (ECHO/MUGA; Section 6.2.6)	X (only C2 ± 7d)									X (± 7d)[h]		
Pregnancy test (FCBP only; Section 6.2.7)	X						X[i]			X[i]	X[i]	

Table 7: Table of Events for Cycles ≥ 2 in Part B (D1-5 Schedule), End of Treatment Visit, and Follow-up Period

	Treatment Period										Follow-up Period	
	Cycles ≥ 2											
	WK1					WK2	WK3	WK4		EOT[b]	Safety[c]	
Events[a]	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 22	Day 28	≤ 28 days	28 days (± 3 days)	Long Term
Pregnancy risk counseling and contraceptive compliance confirmation	X	As specified in Section 6.1.1 and the PPP in Appendix L										
Hematology laboratory (Section 6.2.8)	X	X	X	X	X	X	X	X		X		
Serum chemistry laboratory tests (Section 6.2.8)[j]	X	X				X	X	X		X		
Serum Ca & Mg tests (Section 6.2.8)[j]	X[j]	X[j]	X[j]	X[j]	X[j]							
Serum PTH test (Section 6.2.8)	X				X					X		
Serum P1NP and β-CTx tests (Section 6.2.8)	X									X		
Serum 25-hydroxyvitamin D level (Section 6.2.8)	X											
Urine Ca/ creatinine ratio test (random) (Section 6.2.8)	X				X					X		
Amylase, lipase, T-cell subsets (CD4+ and CD8+), TSH (Section 6.2.8)	X									X		
PT, INR, PTT (for subjects on anticoagulant therapy) (Section 6.2.8)	X									X		
Urinalysis (Section 6.2.8)	X									X		
PK & PD Assessments												
Blood, PK (Section 6.5)[o]				X[o]	X[o]							
Blood (whole), PD biomarker (Section 6.6.2)									X (C2 and C4; ± 3d)	X[n]		Refer to Section 6.3.2

Table 7: Table of Events for Cycles ≥ 2 in Part B (D1-5 Schedule), End of Treatment Visit, and Follow-up Period

Events[a]	Treatment Period										Follow-up Period	
	Cycles ≥ 2											
	WK1					WK2	WK3	WK4		EOT[b]	Safety[c]	
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 22	Day 28	≤ 28 days	28 days (± 3 days)	Long Term
Bone marrow aspirate and biopsy, PD biomarkers & MRD (Section 6.6.3)[l, m]									X (C2 and C4; ± 3d)	X[n]		Refer to Section 6.3.2
SARS-CoV-2 Serology[p] (Section 6.6.4)	Serum collected every 6 months during study treatment (eg, C6D1, C12D1, etc)									X		
Efficacy												
Complete blood counts and examination of peripheral blood smears (Section 6.4)[m]									X (C2 and C4; ± 3d)	X[n]		Refer to Section 6.3.2
Bone marrow aspirate and/or biopsy (Section 6.4)[m]									X (C2 and C4; ± 3d)	X[n]		Refer to Section 6.3.2
Follow-up												
CC-90009-related AE/SAE follow-up	Refer to Section 6.3.1											
Anticancer therapies	Refer to Section 6.3.2											
Survival	Refer to Section 6.3.3											
Transformation to AML for MDS	After signing ICF and until death, lost to follow-up, withdrawal of consent for further data collection, or end of trial.											

Abbreviations: Adverse event = AE; AML = acute myeloid leukemia; β-CTx = beta C-terminal telopeptide; C = cycle; Ca = calcium; CD = cluster of differentiation; D = day; ECHO = echocardiogram; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; FCBP = females of child bearing potential; INR = international normalized ratio; IV = intravenous; LVEF = left ventricular ejection fraction; MDS = myelodysplastic syndromes; Mg = magnesium; MUGA = multi-gated acquisition scan; P1NP = procollagen type 1 N-terminal propeptide; PD = pharmacodynamic; PK = pharmacokinetic; PPP = pregnancy prevention plan; PT = prothrombin time; PTH = parathyroid hormone; PTT = partial thromboplastin time; q = every; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TSH = thyroid-stimulating hormone; WK = week.

[a] All study visits/procedures will have a ± 2 day window and all laboratory blood samples should be drawn predose (≤ 5 hrs), unless otherwise specified in this table or Section 6. Cycles should start ≤ 7 days after the last day of the previous cycle.

[b] EOT Visit performed within 28 days after last dose of CC-90009 for subjects that discontinue prior to completing dosing in Cycle 4. For subjects that complete dosing in Cycle 4, this visit should be completed on Day 28 (± 2 days) of Cycle 4. For subjects who complete dosing after Cycle 4, EOT Visit should be completed within 28 days after the last day of the previous cycle.

[c] Safety Follow-up Visit is performed 28 days (± 3 days) after the last dose of CC-90009 for all subjects. May be performed by telephone contact if pregnancy testing is not required (refer to footnote "i").

[d] Supplements to be administered for at least 3 days after the last dose in each cycle. Supplementation may be prolonged if hypocalcemia occurs (refer to Section 7.2.13.2). Subjects to start supplements at least 3 days prior to Day 1 of Cycles 3 and 4 as per Section 7.2.

[e] Subjects will be closely monitored during the administration of CC-90009 and for at least 1 hour after. Subjects should be adequately hydrated to prevent potential tumor lysis syndrome (TLS) (eg, 2 to 3 liters of oral or IV fluids per day) starting the day prior to CC-90009 administration and continuing through each day of CC-90009 administration. Refer to Section 7.2.12 for information on dose interruptions. The SRC may decide to evaluate alternate dosing schedules (eg, increasing from 5 to up to 10 consecutive days of CC-90009 administration) based on their review of available clinical and laboratory safety data, PK profiles, and PD findings. Subjects should be administered Cycle ≥ 2 of CC-90009 in a Limited Stay Unit (LSU) or as inpatient. Subjects experiencing Grade ≥ 2 hypocalcemia during any cycle should be administered CC-90009 in the inpatient setting for subsequent cycles (an exception can be made for subjects with grade 2 hypocalcemia lasting less than 24 hours that recovers without IV calcium [eg, calcium gluconate or calcium chloride] after discussion with the Celgene medical monitor).

[f] Multiple measurements performed on this day. For subjects who are administered as in-patient in Cycles ≥ 2, on days that CC-90009 is administered, vital signs will be obtained prior to dosing (≤ 3 hours), and 60 minutes (± 15 minutes) and 6 hours (± 1 hr) after the end of the administration of the dose. Starting in Cycle 2 in the outpatient setting, vital signs will be obtained prior to dosing (≤ 3 hours) and at 60 minutes (± 15 minutes) after the end of the administration of the dose. Additional vital signs should be obtained as clinically indicated per the Investigator's medical assessment.

[g] Triplicate ECGs will be performed on Day 1 of each cycle (refer to Section 6.2.5) and a single ECG obtained at the EOT visit.

[h] The EOT Visit LVEF is not required if the prior LVEF was performed within 56 days.

[i] Per the PPP, a pregnancy test is required 28 days after the last dose of for all FCBP. For FCBP with irregular menstrual periods, a pregnancy test is required every 14 days (ie, Day 15 of Cycles ≥ 2 and at 14 and 28 days after the last dose of CC-90009).

[j] In the event of Grade ≥ 2 hypocalcemia or symptoms of hypocalcemia (eg, carpopedal spasm, tetany, seizures, etc), subjects must be hospitalized. Also, if Grade ≥ 2 hypocalcemia and abnormal levels of serum albumin occurs, a serum ionized calcium test must be performed. Refer to Section 7.2.13.2 for hypocalcemia management guidelines. Refer to Section 6.2.8 for required days and timing of tests. Subjects who experienced Grade ≥ 2 hypocalcemia during Cycle 1, require testing Days 1-5 at 6 and 12 hours postdose. All other subjects require testing prior to dosing.

[k] If intra-subject dose escalation occurs, blood samples for PD assays will be collected during the first cycle only at the increased dose; see laboratory manual for details. Multiple blood samples will be collected for this assay on the specified Days 1, 2, 5. Refer to Section 6.6.

[l] Bone marrow samples for biomarker PD assessment are mandatory. When applicable (refer to time points in the table above), bone marrow samples for biomarker PD assessment will be obtained at the same time as a scheduled efficacy assessment. If sufficient bone marrow aspirate specimen is not available, peripheral blood may be submitted in place of the BMA specimen for biomarker studies (eg, MRD); see laboratory manual for details. A bone marrow biopsy can be collected in conjunction with an aspirate if it is standard institutional practice. A bone marrow biopsy must be collected if adequate aspirate sample is not attainable; see for details on sending samples to the central laboratory for disease assessment.

[m] If end of Cycle 2 (Day 28 ± 3 days) samples are obtained on Day 1 of Cycle 3, they must be obtained prior to CC-90009 administration. Additionally, bone marrow aspirates and biopsies may be obtained after a CR is confirmed, if relapse is suspected, or following treatment discontinuation to elucidate effects of long-term treatment or resistance mechanisms. Additional aspirates and biopsies will be collected as clinically indicated based on the Investigator's medical assessment.

[n] For subjects that complete dosing in Cycle 4, performed/obtained once on Day 28 (± 3 days). For subjects that continue (after consultation with Medical Monitor) beyond Cycle 4, efficacy and bone marrow PD assessments may be obtained to confirm a CR, if relapse is suspected, or following treatment discontinuation to elucidate effects of long-term treatment or resistance mechanisms. Additional aspirates and biopsies will be collected as clinically indicated based on the Investigator's medical assessment. Refer to Section 6.3.2 and Section 6.4.

[o] Predose blood sample for both intensive and sparse sampling schedule in Cycles 2-4. Refer to Sections 6.5 and 6.6.

[p] Serum will be collected approximately every 6 months during study treatment and at EOT to be used for possible measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG). Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection.

6 PROCEDURES

Any questions regarding the protocol should be directed to the Celgene Medical Monitor or designee. The procedures conducted for each subject enrolled in the study are outlined in Table 4 and Table 5 for Part A and Table 6 and Table 7 for Part B. All study visits will have a ± 2 day window unless otherwise specified below or in the Table of Events. All laboratory blood samples should be drawn predose unless otherwise specified (eg, PK samples). For subjects enrolled on an alternate schedule (eg, D1-3/D8-10, D1-7, or D1-10 dosing schedules), please refer to Table of Events in Appendix K and Appendices M-O.

The study procedures should be recorded in the source document and the electronic case report forms (eCRF). In the event subjects fail Screening, minimal information will be documented on the eCRFs, per database instructions.

6.1 Screening Period

The Screening window starts 28 days prior to first dose of CC-90009. Refer to Table 4 –Table 7, this section, and Section 6.2 for detailed information on procedures performed and the schedule. For subjects enrolled on an alternate schedule (eg, D1-3/D8-10, D1-7, or D1-10), please refer to Table of Events in Appendix K and Appendices M-O.

Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

Safety laboratory analyses will be performed locally. Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary.

The ICD will be administered at the Screening visit to all subjects by qualified study staff. It must be signed and dated by the subject and the administering staff prior to the start of any other study procedures and its completion documented in source documents and in the eCRF. All screening tests and procedures must be completed within 28 days prior to the first dose of CC-90009 according to the schedule shown in Table 4, Table 6, Table 31, Table 33, Table 35, and Table 37.

Adequate contraceptive methods as specified in the CC-90009 PPP (refer to Appendix L) must be used for at least 28 days before starting CC-90009, while participating in the study, during dose interruptions, and for at least 28 days for FCBP and 28 days for males after the last dose of CC-90009. The PPP applies to all subjects receiving CC-90009 therapy and will be given to sites as a separate document. Subjects will be counseled about appropriate contraception during Screening (refer to Section 6.1.1). Counseling should be documented in source documents.

The following will be performed at Screening, after signed informed consent has been obtained:

- Inclusion and exclusion criteria will be assessed at Screening and recorded in the source documents and the eCRF.
- Pregnancy prevention counseling (refer to Section 6.1.1).
- Medical (including surgical, COVID-19 vaccines, toxicities of prior treatments, known allergies) history, oncologic history, and demographic data (including each subject's date of birth, sex, race, and ethnicity) will be collected during Screening as consistent with local

regulations (eg, if the full date of birth will not be collected but only month and year, age at screening will be collected). Oncologic history will include a detailed history of the primary diagnosis and date, therapies, and responses.

- Information on prior and concomitant medications and procedures will be collected (refer to Section 6.2.1).
- Registration in the integrated response technology system (IRT).
- Adverse event monitoring (refer to Section 10).
- Height and weight measured.
- Vital signs assessed (refer to Section 6.2.3).
- Physical examination (source documented only) and ECOG PS (refer to Section 6.2.4).
- RT-PCR testing for SARS-CoV-2 is mandatory within 7 days prior to first dose of CC-90009 (C1D1). The RT-PCR test should be based on institutional or local guidelines.
- If a subject is identified to have SARS-CoV-2 infection during the screening period, subjects may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:
  - At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR or viral antigen test result, and
  - at least 24 hours have passed since last fever without the use of fever-reducing medications, and
  - acute symptoms (eg, cough, shortness of breath) have resolved, and
  - in the opinion of the investigator, there are no COVID-19 sequelae that may place the participant at a higher risk of receiving investigational treatment.
  - In the instance of a SARS-CoV-2 infection during Screening, the Screening period may be extended beyond the 28-day timeframe with Sponsor Medical Monitor approval; Any Screening tests already performed which could potentially be affected by the SARS-CoV-2 infection or its complications on an individual basis and agreed upon with the Sponsor Medical Monitor (eg, hematology and chemistry labs) should be repeated closer to C1D1.
- A 12-lead ECG in triplicate (refer to Section 6.2.5) will be performed ≥72 hours prior to the first dose of CC-90009 with results received from the central read prior to dosing to fulfill the eligibility criteria.
- Left Ventricular Ejection Fraction (LVEF) assessment (refer to Section 6.2.6).
- Pregnancy β-subunit of human chorionic gonadotropin (β-hCG) test for FCBP as per PPP (refer to Appendix L and Section 6.2.7).
  - As per the PPP, FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting CC-90009. The first pregnancy test must be performed within 10-14 days prior to the start of CC-90009 and the second pregnancy test performed within 24 hours prior to the start of CC-90009. The results must be confirmed to be negative prior to dosing.
- Clinical laboratory tests [hematology, serum chemistry, glucose-6-phosphate dehydrogenase (G6PD), 25-hydroxyvitamin D level, PT, INR, PTT, and urinalysis; refer to Section 6.2.8] are

to be completed within the timeframe specified in Table 4, Table 6, Table 31, Table 33, Table 35, and Table 37.

  - Both a free (ionized) serum calcium test and a corrected serum calcium test (corrected for albumin) should be obtained at Screening to establish baseline values; either may be used to fulfill the inclusion criteria (refer to Section 4.2).
  - Creatinine clearance is determined at Screening.

- Disease (efficacy) assessments (refer to Section 6.4) with the bone marrow aspiration and/or biopsy are collected during Screening within 14 days (Day -14 through Day -1) prior to the first dose of CC-90009. Pharmacodynamic bone marrow biomarker samples are obtained at the same time (refer to Section 6.6.3).
  - In Part A, both bone marrow aspirate and biopsy are mandatory at all time points.
  - In Part B, both a bone marrow aspirate and biopsy should be performed at Screening. Thereafter, bone marrow aspirates are sufficient; a bone marrow biopsy can be collected in conjunction with an aspirate if it is standard institutional practice. A bone marrow biopsy must be collected if adequate aspirate sample is not attainable.
  - In Part B, bone marrow aspirate and/or biopsy, peripheral blood smear, and relevant clinical documentation will be sent to a central lab for analysis and to confirm diagnosis and baseline disease characteristics. Details on timing and quantity of material required will be specified in the laboratory manual. All hematology and bone marrow pathology reports generated by central laboratories and used to establish subject's eligibility will be sent for sponsor review ahead of cohort assignment (if timing allows based on clinical urgency) to provide for any deficiencies in documentation to be addressed.
  - In Part B, on a case-by-case basis and after consultation with the Medical Monitor, it will be determined if local pathology reports can be used to support R/R AML and R/R HR-MDS subjects' eligibility and cohort assignment. Please note that a bone marrow aspirate and/or biopsy sample is still required to be sent to the central laboratory prior to enrollment.
- Pharmacodynamic biomarker blood samples will be collected during Screening within 14 days (Day -14 through Day -1) prior to the first dose of CC-90009 (refer to Section 6.6.2). It is preferable to collect and process these samples on the same day that the bone marrow samples are obtained.
- Eligible subjects will start calcium, calcitriol, and vitamin D supplementation at least 3 days prior to the first dose of CC-90009 in Cycle 1 (refer to Section 7.2). Subjects will be provided with a diary card to record the date and time they take the supplements.

6.1.1 Pregnancy Risk Counseling

The CC-90009 PPP for Celgene Clinical Trials (refer to Appendix L) applies to all subjects receiving CC-90009 therapy and will be given to sites as a separate document.

Qualified healthcare professionals will be trained by Celgene, or designee, in the requirements specific to contraceptive counseling of subjects. Once trained these healthcare staff will counsel subjects prior to the administration of CC-90009 and at the beginning of each subsequent cycle to ensure that the subject has complied with all requirements including use of birth control and that the subject understands the risks associated with CC-90009. This step will be documented with a

completed Education and Counseling Guidance Document, and CC-90009 will not be administered until this step occurs.

Per the PPP, the Investigator must confirm with the subject at each visit that their methods of birth control follow the PPP or confirm the subject's commitment to complete abstinence.

A CC-90009 Information Sheet will be provided to each subject before the first dose of CC-90009.

6.2 Treatment Period

All subjects who fulfill the inclusion/exclusion criteria who are continuing in the study will be registered in the IRT system prior to receiving CC-90009 on Day 1 of Cycle 1.

All subjects will be required to start calcium, calcitriol, and vitamin D supplementation at least 3 days prior to the first dose of CC-90009 in each cycle and continue until ≥ 3 days after the last dose of CC-90009 in each cycle (eg, ≥ Day 8 when CC-90009 is administered on Days 1-5, ≥ Day 10 when CC-90009 is administered on Days 1-7, or ≥ Day 13 when CC-90009 is administered on Days 1-3/8-10 or Days 1-10). Supplementation may be extended if hypocalcemia occurs (refer to Section 7.2.13.2). Subjects will document taking the supplements on diary cards that will be reviewed on Day 1 of each cycle and at the EOT visit. Subjects should be adequately hydrated (eg, 2 to 3 liters of oral or IV fluids per day) starting the day prior to CC-90009 administration and continuing through each day of CC-90009 administration. Refer to Section 7.2 and Section 8.3 for detailed information.

6.2.1 Concomitant Medication and Procedures

All concomitant medications and procedures taken or conducted beginning when the subject signs the ICD, throughout the study, and until 28 days after the last dose of CC-90009 will be recorded in the source documents and eCRF.

6.2.2 Adverse Event Monitoring

Adverse events (AEs) and serious adverse events (SAEs) will be recorded from the time a subject signs the ICD until 28 days after the last dose of CC-90009.

Subjects experiencing AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the Investigator (refer to Section 10 for detailed information). Every attempt will be made to document resolution dates for ongoing AEs. The AEs will be recorded on the AE page of the eCRF and in the subject's source documents.

6.2.3 Vital Signs and Weight

Vital signs include body temperature, blood pressure, pulse rate, and respiration rate and will be recorded at Screening and during the study at various time points for safety monitoring as described in Table 4 – Table 7, Events in Appendix K and Appendices M-O.

In Cycle 1 and for subjects who are administered as in-patient in Cycles ≥ 2, on days that CC-90009 is administered, vital signs will be obtained prior to dosing (≤ 3 hours), and at 60 minutes (± 15 minutes) and 6 hours (± 1 hr) after the end of the administration of the dose. Starting in Cycle 2 in the outpatient setting, vital signs will be obtained prior to dosing (≤ 3 hours) and at 60 minutes (± 15 minutes) after the end of the administration of the dose. Additional vital signs should be

obtained as clinically indicated per the Investigator's medical assessment. Recorded measurements will be captured in the source document and eCRF. The subject's weight will be recorded in the source document and eCRF at the visits listed in Table 4 – Table 7, Events in Appendix K and Appendices M-O.

6.2.4 Physical Examination and ECOG Performance Status

Complete physical examination and ECOG PS (refer to Appendix C) will be performed at the visits listed in Table 4 – Table 7, Appendix K, and Appendices M-O. Results for both will be recorded in the source document. Results for the ECOG PS will also be collected on the eCRF.

Physical examination findings will be classified as either normal or abnormal. If abnormal, a description of the abnormality and clinical importance will be provided in the source documents. Clinically significant changes from baseline will be recorded in the AE section of the eCRF.

6.2.5 12-Lead Electrocardiograms

Triplicate standard 12-lead ECGs will be recorded at the visits listed in Table 4 –Table 7, Appendix K, and Appendices M-O. The 12-lead ECGs (12-lead at 25 mm/sec reporting rhythm, ventricular rate, PR interval, QRS complex, QT interval, and QTc interval) will be performed after the subject has been in the supine position for at least 5 minutes. If the scheduled time for an ECG coincides with a PK blood collection, the blood draw should be performed as scheduled, with the ECG being performed prior to the blood collection.

Triplicate ECGs (3 recordings within 2 ± 1 minute intervals) will be performed at:

- Screening (≥ 72 hours prior to Day 1 with results received from the central ECG laboratory prior to the first dose of CC-90009)
- Cycle 1, Day 1
  - Predose (≤ 60 minutes prior),
  - Post-end of infusion (EOI) at 30 minutes (± 5 minutes), 2 hours, 4 hours, and 8 hours (each ± 30 minutes) [timings are given in reference to the end of the infusion]
- Cycle 1, Day 5 (D1-5 schedule only) or Cycle 1 Day 7 (D1-7 schedule only)
  - If C1D5 or C1D7 is a dosing day, predose (≤ 60 minutes prior) and 30 minutes (± 5 minutes) after the EOI
  - If C1D5 or C1D7 is not a dosing day (eg, D1-3/D8-10 schedule), no ECG done
  - If enrolled on the D1-10 schedule, no ECG done on C1D5 or C1D7
- Cycle 1, Day 8 (C1D8)
  - If C1D8 is a dosing day, predose (≤ 60 minutes prior) and 30 minutes (± 5 minutes) after the EOI
  - If C1D8 is not a dosing day, single time point
- Cycle 1, Day 10 (C1D10)
  - If C1D10 is a dosing day, predose (≤ 60 minutes prior) and 30 minutes (± 5 minutes) after the EOI
  - If C1D10 is not a dosing day (eg, D1-5 or D1-7 schedules), no ECG done

- Cycles ≥ 2, Day 1
  - predose (≤ 60 minutes prior)

A single ECG will be performed at the EOT visit.

During the Treatment Period, Investigators will make immediate clinical decisions based on their interpretation of the ECG results and provide their overall assessment of the ECG in the eCRF. Clinically significant changes from baseline will be recorded in the AE section of the eCRF.

The ECG outputs will also be uploaded to the central ECG laboratory for definitive analysis and interpretation.

6.2.6 Left Ventricular Ejection Fraction

Left ventricular ejection fraction (LVEF) will be assessed by MUGA scan or ECHO at Screening in all subjects (not required if an assessment has been performed within 28 days prior to the start of study treatment). Follow-up assessments are required as indicated in Table 5, Table 7, Table 32, Table 34, Table 36, or Table 38. Follow-up assessments should use the same procedure used at the screening assessment. A clinically significant reduction is defined as either a ≥ 20% absolute reduction in LVEF or drop to below 45%.

6.2.7 Pregnancy Testing

A FCBP is defined as a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy, or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

The Investigator will classify a female subject as a FCBP according to this definition. Pregnancy testing is not required for non-FCBP subjects but justification must be recorded in the eCRF and the source document. Pregnancy testing will be conducted by the local laboratory.

For a FCBP, pregnancy testing will be conducted at the visits listed in Table 4 – Table 7, Appendix K, or Appendices M-O as outlined in the PPP (refer to Appendix L).

Results for pregnancy tests will be recorded in the source document and eCRF.

6.2.8 Clinical Laboratory Tests

The following laboratory assessments will be performed at the Screening visit and during the study at the time points as described in Table 4 – Table 7, Appendix K, and Appendices M-O. All samples on dosing days should be drawn predose (≤ 5 hours prior) unless otherwise specified. Laboratory assessments will be recorded in the source document and eCRF and are the following:

- Hematology: CBC including hemoglobin, hematocrit, red blood cell count with indices, WBC count with absolute differential (including blast count) and platelet count.
- Serum chemistry: albumin, total protein, bicarbonate or carbon dioxide (CO_2), corrected calcium (corrected for albumin), C-reactive protein (CRP), ferritin, magnesium, phosphorus, creatinine, urea/blood urea nitrogen (BUN), glucose (fasting ≥ 4 hours), potassium, sodium,

chloride, total bilirubin (fractionate if outside normal range), alkaline phosphatase, AST (SGOT), ALT (SGPT), LDH, and uric acid.

- Additional monitoring for TLS (bicarbonate or CO2, phosphorous, creatinine, urea/BUN, potassium, sodium, chloride, LDH, and uric acid) performed in Cycle 1 on Days 1, 2, and 3 at 12 hours (± 1 hour) postdose.
- Additional serum Ca (corrected for albumin) and Mg tests performed in Cycle 1 on dosing days at 6 and 12 hours (± 1 hour) postdose and in Cycles ≥ 2 prior to dosing. For subjects experiencing Grade ≥ 2 hypocalcemia in Cycle 1, additional serum Ca (corrected for albumin) and Mg tests will be performed all dosing days at 6 and 12 hours (± 1 hour) postdose in Cycles ≥ 2. Additional serum PTH tests performed in Cycle 1 on dosing days at 6 hours (± 1 hour) postdose.

  NOTE: In the event of Grade ≥ 2 hypocalcemia and abnormal levels of serum albumin, a serum ionized calcium test and more frequent calcium monitoring must be performed (refer to Section 7.2.13.2). Hypocalcemia adverse event grading should be reported as the highest grade determined.

- G6PD at Screening only
- Special calcium metabolism monitoring tests:
  - serum PTH, total P1NP, and serum β-CTx
  - urine calcium/creatinine ratio obtained from spot (random) urine collection
- Serum 25-hydroxyvitamin D level
- Special chemistry: amylase, lipase, T-cell subsets (cluster of differentiation [CD]4+ and CD8+), thyroid-stimulating hormone (TSH; if abnormal reflex to free thyroxine)
- Coagulation: PT, INR, and PTT at Screening and only repeated during the study for subjects on anticoagulation therapy as shown in Table 5, Table 7, Table 32, Table 34, Table 36, or Table 38 and as clinically indicated.
- Urinalysis: dipstick
  - microscopy in the event of a positive (1+ or greater) blood or protein
  - 24-hour collection for creatinine clearance and protein quantification in the event of 2+ or greater protein
- Creatinine clearance determination required at Screening to fulfill inclusion criteria (refer to Section 4.3).

6.2.9 End of Treatment

An EOT evaluation (refer to Table 5, Table 7, Table 32, Table 34, Table 36, or Table 38 for procedures) will be performed for subjects who are withdrawn from treatment for any reason as soon as possible (≤ 28 days) after the decision to permanently discontinue treatment has been made. For subjects who complete dosing in Cycle 4, this visit should be completed on Day 28 (± 2 days) of Cycle 4.

6.3 Follow-up Period

6.3.1 Safety Follow-up

All subjects will be followed for 28 days after the last dose of CC-90009 for AE reporting and concomitant medication information. The 28-day (± 3 days) safety follow-up contact may be by telephone. In addition, any SAEs made known to the Investigator at any time thereafter that are suspected of being related to CC-90009 will be reported as described in Section 10.1. Subjects will be followed for all SAEs and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the subject is lost to follow-up, or for suspected cases, until SARS-CoV-2 infection is ruled-out.

Pregnancy testing will be performed per the PPP and Table 5, Table 7, Table 32, Table 34, Table 36, or Table 38.

6.3.2 Efficacy Long Term Follow-up

Subjects without documented progression of disease (or relapse) or start of new anti-cancer therapies will have efficacy evaluations of complete blood counts and peripheral blood smears performed every subsequent 8 weeks (± 1 week) for the 1st year and every 12 weeks (± 2 weeks) for the 2nd year or until progression of disease (or relapse), initiation of a new anticancer therapy, withdrawal from the study, death, or the End of Trial, whichever comes first. A bone marrow evaluation will be completed at the end of the 1st year and as clinically indicated during the Follow-up Period.

Information (including dates) on new anticancer therapies initiated will be collected until progression of disease (or relapse), withdrawal from the study, death, or the End of Trial, whichever comes first.

Information will also be collected on any study drug-related SAEs.

6.3.3 Survival Follow-up

After the Safety Follow-up visit, all subjects will be followed according to the schedule for the efficacy long term follow-up (refer to Section 6.3.2) for survival for up to 2 years or until death, lost to follow-up, or the End of Trial, whichever occurs first. Survival follow-up may be conducted by record review (including public records) and/or telephone contact with the subject, family, or the subject's treating physician.

6.4 Efficacy Assessment

Disease assessments by bone marrow aspiration and biopsy, along with complete blood counts and examination of peripheral blood smears will be performed as indicated in Table 4 – Table 7, Appendix K, or Appendices M-O. In addition, bone marrow aspirates and biopsies must be collected in order to confirm CR or morphologic CR with incomplete blood recovery (CRi) and morphologic CR with partial hematologic recovery (CRh), relapse after CR, CRi, or CRh (as assessed by the Investigator based on CBC with WBC differential results), or disease progression. If disease progression features are observed following the bone marrow evaluation, a repeat bone

marrow evaluation should be performed one month later to confirm disease progression (as described below). Additional aspirates and/or biopsies will be collected as clinically indicated (eg, Cycle 1 Day 15, based on Investigator's medical assessment).

Progressive disease will be defined as:

- A > 50% increase in bone marrow blast count percentage from the baseline (screening) bone marrow blast count that persists for at least 2 bone marrow assessments separated by at least 1 month, unless the baseline bone marrow blast count is > 70%, in which case, a finding of > 70% blasts that persists for 2 post baseline bone marrow assessments separated by at least 1 month would be considered progression, or
- A doubling of the baseline absolute peripheral blood blast count that persists for ≥ 7 days and the final absolute peripheral blood blast count is > 10 x 10^9/L.

The date of progressive disease is defined as the first date that there was either a > 50% increase in bone marrow blast count from baseline, a persistence of bone marrow blasts > 70% in subject with a baseline bone marrow blast count of > 70%, or a doubling of the peripheral blood blast count.

Treatment failure will be defined as progressive disease or not achieving at least partial remission (PR) by the end of the treatment period. In the absence of progressive disease (as defined above) or unacceptable toxicity, subjects may continue treatment with CC-90009 through Cycle 4 if they are deriving benefit, as judged by the Investigator. Failure to achieve a response and not meeting the criteria for progressive disease will be considered stable disease. Additional cycles of treatment beyond Cycle 4 may be allowed after discussion with the Medical Monitor if the subject is demonstrating clinical benefit (stable disease or PR or CR) and if tolerating the study drug without unacceptable toxicity.

Bone marrow aspirates and biopsies are to be evaluated for morphology, flow cytometry, karyotype, and molecular studies (eg, *FLT3, KIT, NPM1*, *CEBPα* mutational status if positive on previous bone marrow biopsies). In Part B, bone marrow analyses will be performed at a central laboratory. Molecular and cytogenetic studies may be omitted at the:

- Screening bone marrow evaluation, if they were completed within the prior 90 days and the results are available to enter on the eCRFs,
- Part A, Cycle 1 Day 42 ± 3 days (or at time of hematologic recovery) bone marrow evaluation for subjects with extended safety monitoring in Cycle 1 if a complete response is documented on Day 28.

The marrow aspiration and core sampling (biopsy) should be performed according to the standard of care and analyzed at the local site's laboratory in accordance with the International Council for Standardization in Hematology (ICSH) Guidelines (Lee, 2008).

The clinical activity of CC-90009 will be evaluated by the Investigator by assessing response to treatment according to the IWG Response Criteria in AML (Cheson, 2003; refer to Appendix C).

Treatment decisions will be based on Investigator's assessment. MDS response will be based on the IWG Response Criteria for Myelodysplasia (Cheson, 2006; refer to Appendix G).

Subjects who discontinue treatment for reasons other than disease progression (or relapse), start of a new anticancer therapy, or withdrawal of consent from the entire study will have disease assessments performed up to a maximum of 2 years according to the specified assessment schedule (refer to Section 6.3.2) until progression and/or initiation of new systemic anticancer therapies.

6.5 Pharmacokinetics

6.5.1 Blood Collection for PK Analysis

In Part A, intensive blood samples will be collected from all subjects for evaluation of PK of CC-90009 in plasma at time points specified in Table 40, Table 41, Table 42, or Table 43. In Part B, intensive blood samples will be collected from approximately 10 selected subjects in each cohort for evaluation of PK of both CC-90009 and hydroxypropyl-β-cyclodextrin in plasma; sparse blood samples will be collected from the remaining subjects for evaluation of PK of CC-90009. Time points are specified for intensive and sparse PK sampling, respectively in Table 44 or Table 8.

The concentration of R- and S-enantiomers of CC-90009, ie CC0782618 (R-enantiomer) and CC0782619 (S-enantiomer), in plasma will be determined by LC/MS. The CC-90009 concentration will be calculated as a sum of its R- and S-enantiomers. An exploratory analysis of CC-90009 metabolites in plasma may be performed utilizing the blood samples collected for PK evaluation.

The blood PK samples at 2, 15, and 30 minutes after the EOI MUST be collected from the arm contralateral to the arm used for CC-90009 administration. If a peripheral IV catheter is used for the CC-90009 IV administration, the PK samples should be obtained from the opposite arm. In general, blood for PK samples should not be drawn from a central line. If a peripheral line is not accessible, blood for PK samples drawn from a central line MUST be collected after the lumen is flushed with saline, and the non-dosing lumen of a dual/triple lumen catheter should be used. Administration and PK blood draw locations will be recorded in the database.

Table 8: Blood Pharmacokinetic Sampling Schedule in Part B: 2.4 and 3.0 mg Days 1-7 Schedule

Time Relative to CC-90009 Administration	Collection Window	Intensive	Sparse
Cycle 1 Day 1 and Cycle 1 Last Dose			
0	≤ 30 minutes prior to start	X	
Mid-infusion (eg, at 15 minutes in a 30 minute infusion)[a]	± 1 minute	X	
15 minutes after EOI	± 5 minutes	X	
30 minutes after EOI	± 5 minutes	X	X
1 hour after EOI	± 5 minutes	X	X
2 hours after EOI	± 10 minutes	X	
4 hours after EOI	± 10 minutes	X	X
8 hours after EOI	± 30 minutes	X	
12 hours after EOI	± 2 hours	X	
24 hours after EOI	± 3 hours	X[b]	Xb
Cycles 2-4			
Second to last dosing day, pre-dose	≤ 30 minutes prior to start	X	X
Last dosing day, pre-dose	≤ 30 minutes prior to start	X	X

Abbreviation: EOI = end of infusion/injection.

[a] In cases where the only access for drug administration is the central line, mid-infusion PK draws may be omitted.

[b] 24 hours after EOI on day 1 occurs on Day 2. Must be drawn prior to the administration of CC-90009 on Day 2.

The following information must be captured in the eCRFs:

- The dose level and total dose administered.
- The actual clock time of the start of the CC-90009 IV administration.
- The actual clock time of the EOI.
- The actual clock time of each PK sample collection.
- The location of drug administration and PK sample collection.

The Sponsor may conduct additional analyses on the PK samples in order to follow-up the safety of the study treatment or to better understand the progression of the disease or the disease's response to the study treatment.

See the Laboratory Manual for sample collection, handling, and processing instructions.

6.5.2 Urine Collection for PK Analysis

Urine will be collected in approximately 10 evaluable subjects in Part A and/or Part B. Collection will occur on Cycle 1 Day 1. Urine will be collected predose (within approximately 60 minutes prior to dosing; spot collection to serve as the blank control) and then pooled as a single block over the intervals of 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours postdose. Within approximately 15 minutes of ending each collection interval, subjects should empty their bladder prior to the start of each new collection interval. This urine should be added to the pooled urine for the current collection interval. During each collection interval, all urine voided must be collected (ie, no urine should be allowed to pass into the toilet). Incomplete collection or missed samples will be recorded as a deviation.

The concentration of CC-90009 and hydroxypropyl-β-cyclodextrin in urine will be determined. An exploratory analysis of CC-90009 metabolites in urine may be performed utilizing the urine samples collected for PK evaluation.

The following information must be captured in the eCRFs:

- The dose level and total dose administered.
- The actual clock time of the start and end of the CC-90009 IV administration.
- The actual clock time of the start and end of each urine collection interval.
- The weight of urine collected during each collection interval (eg, 200 g during the 0 to 4 hours postdose collection interval).

See the Laboratory Manual for sample collection, handling, and processing instructions.

6.6 Biomarkers, Pharmacodynamics, Pharmacogenomics

6.6.1 Pharmacogenomics Sample

A sample (eg, buccal swab or nail clippings) will be collected prior to dosing on Cycle 1 Day 1 for assessment of potential pharmacogenomics markers of CC-90009 safety, activity or exposure.

6.6.2 Pharmacodynamic Biomarker Blood Samples

The schedules for blood collections for pharmacodynamic biomarkers are provided in Table 9 and Table 10.

Table 9: Sample Collection of Blood for Pharmacodynamic Biomarkers on D1-5 Schedule and Alternative Schedules with up to 10 consecutive dosing days (eg, D1-7 and D1-10) for Part A or Part B

Sample	Screening	Cycle 1[a]										
		Day 1		Day 2		Day 3		Day 4	Last Day of Dosing	Day 8[b]	Day 15	Day 28[d]
	Day -14 to -1[c]	Predose (≤ 3 hrs)	6 hours (± 15 min) after EOI	Predose (≤ 3 hrs)	6 hours (± 15 min) after EOI	Predose (≤ 3 hrs)	6 hours (± 15 min) after EOI	Predose (≤ 3 hrs)	6 hours (± 2 hr) after EOI	AM	AM	AM
Whole blood, flow cytometry[a]	X	X	X	X[g]	X[g]	X	X			X	X[g]	X
Whole blood, PD biomarkers	X[d]								X[d,e]			X[d,e]
Blood for PBMC, PD protein & RNA[a]	X	X		X[g]		X				X		
Blood for PBMCs, ex vivo sensitivity assays, phenotyping & sequencing		X										
Blood for plasma, cytokine assays	X	X		X		X		X		X		
SARS-CoV-2 Serology[f]		X										

Abbreviations: AM = morning; EOI = end of infusion/injection; PBMC = peripheral blood mononuclear cells; PD = pharmacodynamic; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

a If intra-subject dose escalation occurs, blood samples for PD assays will also be collected during the first cycle at the increased dose on Days 1, 2, 3, 4, 8 and 15; see laboratory manual for details.

b If Day 8 is a dosing day due to use of an alternate schedule per the SRC, obtain samples pre-dose.

c Obtaining the Screening samples on the same day as the Screening bone marrow aspirate and biopsy is preferred.

d For subjects in Part B only. Last day of dosing is defined as the last consecutive planned day (eg, Day 5 on the Days 1-5 schedule or Day 7 of the Days 1-7 schedule). See also footnote e and Section 6.6.3 for allowable days for the Cycle 1 Last Day of Dosing sample collection (ie, on Days 1-5 schedule, Day 4 or 5; on Days 1-7 schedule, Day 6, 7, or 8).

e Collected the same day the bone marrow samples are collected for PD or response assessments in Cycles 1, 2 and 4

f Serum collected to be used for possible measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG (see Table 6)

g For Part A only.

Table 10: Sample Collection of Blood for Pharmacodynamic Biomarkers using the Alternate D1-3/D8-10 Schedule for Part A or Part B

Sample	Screening	Cycle 1								
		Day 1		Day 2	Day 3	Day 4	Day 8	Day 9	Day 15	Day 22
	Day -14 to -1[a]	Predose (≤ 3 hrs)	6 hours (± 15 min) after EOI	Predose (≤ 3 hrs)	Predose (≤ 3 hrs)	AM	Predose (≤ 3 hrs)	Predose (≤ 3 hrs)	AM	AM
Whole blood, flow cytometrya	X	X	X	X	X		X	X	X	X
Blood for PBMC, PD protein & RNA[a]	X	X		X		X	X	X		
Blood for PBMCs, ex vivo sensitivity assays, phenotyping & sequencing		X								
Blood for plasma, cytokine assays	X	X		X	X	X	X	X	X	

Abbreviations: EOI = end of infusion/injection; PD = pharmacodynamic; RNA = ribonucleic acid.

[a] Obtaining the Screening samples on the same day as the Screening bone marrow aspirate and biopsy is preferred.

6.6.3 Pharmacodynamic Biomarker Bone Marrow Samples

Bone marrow aspirates and biopsy for PD and prognostic/predictive biomarkers will be collected at the time points indicated in Table 4 – Table 7, Appendix K, or Appendices M-O. Exploratory tests may be performed to determine Minimal Residual Disease (MRD) status at efficacy time points. In Cycle 1 on Day 5 on the D1-5 dosing schedule, the PD samples will be collected between 4 to 8 hours after CC-90009 is administered. If necessary due to scheduling conflicts, the PD samples may be collected on Day 4 (4 to 8 hours after dosing). If the dosing interval (schedule) is extended, then samples will be obtained on the last day ± 1 day (ie, if extended to consecutive 7 days or 10 days, the PD bone marrow sample can be collected on Day 6-8 [Appendix M] or 9-11 [Appendix O]). For the D1-3/D8-10 schedule, the PD bone marrow sample is collected on Day 9 or 10 (Appendix K).

Additionally, bone marrow aspirates and/or biopsies may be obtained in both Part A and Part B, after a CR is confirmed, if relapse is suspected, or following treatment discontinuation to elucidate effects of long-term treatment or resistance mechanisms, or as clinically indicated based on the Investigator's medical assessment. When obtained for any of the reasons above, samples for biomarker assessments will also be collected at the same time.

6.6.4 SARS-CoV-2 Serology Samples

Serum and plasma samples may be assessed by enzyme-linked immunosorbent assay, seromics, ctDNA measurements, metabolomics, and/or other relevant multiplex-based protein assay methods for immune-related factors that may be associated with efficacy or AEs; such factors may include, but are not limited to, assessments of cytokines, chemokines, inflammatory factors, SARS-CoV-2 serologic status, and ctDNA. Serum will be collected predose on Cycle 1 Day 1 (or at screening), approximately every 6 months during study treatment and at EOT to be used for possible measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG). Serum should also be collected approximately 4 weeks after documented or suspected SARS-CoV-2 infection (see Table 6 – Table 7 and Table 35 – Table 36).

6.6.5 All Pharmacodynamic and Pharmacogenomics Samples

Refer to the Laboratory Manual for sample collection, handling, and processing instructions.

The Sponsor may conduct additional analyses on the biomarker samples in order to follow up the safety of the study treatment or to better understand the progression of the disease or the disease's response to the study treatment or the subject's predisposition to therapeutic response to CC-90009.

6.7 Additional and Optional Research

Additional and optional research as described below may be performed using left-over samples originally collected for another test required in this study or using samples collected specifically for biomarker testing. The research may involve genetic tests using DNA or RNA and may lead to the development of new diagnostic tests.

6.7.1 Additional Research

Additional research related to the study drug and/or disease may be performed. The results of this additional research could help to improve the diagnosis and/or the treatment of this disease in the future.

6.7.2 Optional Research

Optional research not related to the study drug or the subject's disease may be performed. The subject's decision to participate in this optional research will not impact their ability to participate in the main study.

6.8 Subject Reported Outcomes

Not Applicable

7 DESCRIPTION OF STUDY TREATMENT

7.1 Description of Investigational Product

7.1.1 Physical Properties

CC-90009 has a molecular weight of 461.85 g/mole. It is a white to off-white powder.

7.1.2 Formulation

Celgene Corporation will supply CC-90009 clinical drug product as a lyophilized powder for reconstitution to solution in single-use vials and it should be stored per the product label. The drug product is available in two different formulations: Gen 1 and Gen 2b. The study will initially employ Gen 1 (DL1: 0.3 mg, DL2: 0.6 mg, and DL3: 1.2 mg), and then during dose escalation, Gen 2b was introduced at DL4 (2.4 mg) to replace the Gen 1 formulation. Each vial of Gen 1 CC-90009 contains 1.05 mg of CC-90009, 18.6 mg anhydrous citric acid, 18.5 mg anhydrous sodium citrate, and 252.0 mg of Kleptose™ hydroxypropyl beta-cyclodextrin (HPBCD) as a freeze dried powder. CC-90009 is slightly hygroscopic. Each vial of Gen 2b formulation of CC-90009 contains 1 mg CC-90009 and 800 mg hydroxypropyl-beta-cyclodextrin (HPBCD) as a freeze dried powder. CC-90009 clinical drug product is packaged in a 20 mL US Pharmacopeia (USP) Type I glass vial or local equivalent. The CC-90009 vial does not contain any preservative and is for single use only. CC-90009 should be prepared according to the package instructions, the CC-90009 Pharmacy Manuals, and local practice regulations. Gen 1 formulation is reconstituted in sterile Water for Injection (SWFI). Gen 2b formulation is reconstituted in 0.45% sodium chloride (half strength normal saline) and further diluted in 0.9% sodium chloride (normal saline) for injection (eg, for infusion doses between 0.6 and 10 mg, Gen2b formation is reconstituted with 4.5 mL of 0.45% sodium chloride [half strength normal saline] to a concentration of 0.2 mg/mL The reconstituted solution can be further diluted in 0.9% sodium chloride [normal saline] to achieve a 50 mL volume.)

DMA is a process solvent used during manufacture of Gen 1 formulation of CC-90009 that is removed during processing. The daily dose of DMA residual solvent in Gen 1 CC-90009 must not exceed the ICH permitted daily exposure limit (10.9 mg/day) to proceed with dose escalation above a CC-90009 daily dose of 2.4 mg. Gen 2b CC-90009 was developed to enable doses above the limits imposed on Gen 1 formulation. Gen 2b CC-90009 is permitted at doses up to 20 mg CC-90009 per day. The SRC determined the dose cohort for introduction of Gen 2b CC-90009 during Part A of the study to be DL4: 2.4 mg on Days 1-5.

Females of childbearing potential and fertile males should not handle or administer CC-90009 unless they are wearing gloves.

7.2 Treatment Administration and Schedule

CC-90009 will be administered QD on Days 1 to 5 (on the D1-5 dosing schedule) of Cycles 1 to 4. Subjects will be closely monitored throughout the administration of CC-90009 and for 1 hour following each administration. In addition, subjects will be admitted as inpatients for each administration of CC-90009 and monitoring in Cycle 1. For Cycles ≥ 2, subjects will either be admitted as inpatients or treated/monitored in a LSU per Investigator's discretion. Subjects with

Grade ≥ 2 hypocalcemia in any cycle should be treated as inpatients in subsequent cycles (an exception can be made for subjects with grade 2 hypocalcemia lasting less than 24 hours that recovers without IV calcium [eg, calcium gluconate or calcium chloride] after discussion with the Celgene medical monitor). The SRC may evaluate modified dosing schedules (eg, increasing from 5 to up to 10 consecutive days of dosing, intermittent schedules or longer infusion times) in additional cohorts, if necessary, based on toxicity, PK profiles, and PD findings.

For CC-90009 doses at or above 3.6 mg, all subjects will receive a dose of steroids (eg, dexamethasone 10 mg IV (or by mouth [PO] or equivalent) 30 min to 3 hrs prior to each daily dose of CC-90009 (Table 4 –Table 7, Appendix K, or Appendices M-O). For CC-90009 dosed at 3.0 mg on the Days 1-7 and Days 1-10 dosing schedules, steroid premedication is recommended for each of the dosing days. On these schedules with longer dosing days, a lower dose of dexamethasone may be given (minimum of 4 mg) per Investigator's judgement based on the subject's expected tolerability of corticosteroids. The frequency and/or the dose of dexamethasone (or equivalent) administration may be modified based on evaluation and recommendation by the SRC (eg, D1-5, D1-7, D1-10, or D1, D3, D5).

All subjects will be required to start calcium, calcitriol, and vitamin D supplementation at least 3 days prior to the first dose of CC-90009 in each cycle and continue until ≥ 3 days after the last dose of CC-90009 in each cycle (eg, ≥ Day 8 when CC-90009 is administered on Days 1-5, ≥ Day 10 when CC-90009 is administered on Days 1-7, or ≥ Day 13 when CC-90009 is administered on Days 1-3/8-10 or Days 1-10). Supplementation may be extended if hypocalcemia occurs (refer to Section 7.2.13.2). The time and date of administration will be recorded on a diary card.

The calcium/calcitriol/vitamin D supplementation regimen is:

- Calcium carbonate 500 mg elemental calcium PO 3 times a day (TID) (taken after meals to increase absorption)
  - Alternative preparations of calcium can be substituted but they must equal at least 1200 mg of elemental calcium per day given in divided doses (eg, TID).
  - If the subject is on a proton pump inhibitor (PPI) or has gastric achlorhydria, then administer calcium citrate 630 mg elemental calcium PO TID
- Calcitriol 0.25 micrograms PO QD
- Vitamin D supplementation is based on the Screening serum 25-hydroxyvitamin D level:
  - Level < 12 ng/mL – excluded from the study
  - Level 12 – 20 ng/mL – Vitamin D3 or D2 50,000 IU weekly
  - Level > 20 ng/mL– Vitamin D3 or D2 1000 IU QD

The risk of TLS with CC-90009 is unknown. Subjects should be adequately hydrated (eg, 2 to 3 liters of oral or IV fluids per day) starting the day prior to CC-90009 administration and continuing through each day of CC-90009 administration. Medications to prevent or treat TLS are permitted (refer to Section 8.1).

In the absence of progressive disease (as defined in Section 6.4) or unacceptable toxicity, subjects may continue treatment with CC-90009 for a maximum of 4 cycles if they are deriving benefit, as judged by the Investigator.

7.2.1 CC-90009 Preparation and Administration

Prior to administration, CC-90009 must be reconstituted using aseptic technique. The reconstituted solution for IV administration may be stored at 5°C for up to 8 hours or room temperature for up to 4 hours. Total storage time of final diluted product in syringe or IV bag should not exceed 4 hours at room temperature (20-25ºC). Administration must be completed within the allowed storage time after reconstitution. If you store CC-90009, source documentation must be kept to demonstrate correct temperature was maintained during the storage period and the storage time after reconstitution was within the protocol limits.

Gen 1 CC-90009 is administered as an IV push (≤ 1 minute). Gen 2b CC-90009 should be administered as an IV infusion (eg, 30 ± 5 minutes). The SRC may recommended alternate administration guidelines based on review of available clinical and laboratory safety data, PK profiles, and PD findings. Refer to the CC-90009 Pharmacy Manuals for detailed information on the preparation and administration of CC-90009. The start time, stop time, and infusion rate (if applicable) of each CC-90009 administration will be recorded in the source documents and on the eCRF.

7.2.2 Dose Escalation Criteria

Cohorts of one or more subjects each will be given CC-90009 at doses that will increase in 100% increments per cohort until ≥ 2 subjects experience a CC-90009-related Grade ≥ 2 adverse event (may be different cohorts) in the DLT window, or ≥ 1 subject experiences a DLT within the DLT window. At that time the current cohort and all subsequent cohorts will be expanded enrolling 3 to 6 subjects (mandatory increase to 6 subjects if a DLT occurs). A dose escalation schedule with dose increments not to exceed 50% will concurrently be initiated in order to establish the NTD and MTD. The number of cohorts depends on incidence of DLT. A subject may experience more than one DLT. Dose escalation decisions are based on the number of subjects experiencing DLT events. The initial dose will be 0.3 mg.

Dose escalation decisions will be made at the discretion of the SRC. The SRC may decide to evaluate a higher dose cohort, additional subjects within a dose cohort, intermediate dose cohorts, smaller dose increments, alternate dosing schedules (eg, increasing from 5 to up to 10 consecutive days of CC-90009 administration), and/or declare an MTD based on their review of available clinical and laboratory safety data, PK profiles, and PD findings.

In the event that an alternate dosing schedule is evaluated, the starting dose and schedule will not exceed the dose intensity of a dose cohort that has previously met the criteria for dose escalation (Figure 3). Refer to Section 3.1.

Dose reduction and temporary delay of CC-90009 dosing due to toxicity is allowed, but dose reduction during Cycle 1 will constitute DLT.

7.2.3 Definition of a Subject Evaluable for DLT

All subjects who receive at least one dose of CC-90009 will be evaluable for safety.

After the first dose is administered in any cohort of subjects during dose escalation, subjects in each cohort are observed for at least 28 days and up to 42 days (Cycle 1, DLT window) before the next higher, protocol-specified dose cohort can begin. A subject evaluable for DLT is defined as one that:

- Has received at least 80% of the total planned Cycle 1 dose (eg, ≥ 4 CC-90009 doses for the Days 1-5 schedule to be completed on or before Day 10, ≥ 6 CC-90009 doses for the Days 1-7 schedule to be completed on or before Day 10, ≥8 doses by Day 14 for the Days 1-10 schedule, or ≥ 5 doses by Day 14 for the D1-3/D8-10 schedule) of CC-90009 during Cycle 1 without experiencing a DLT,

  Or
- Experienced a DLT after receiving at least one dose (or fraction thereof) of CC-90009.

In the event that an alternate dose schedule (eg, increasing from 5 days to up to 10 consecutive days of dosing) is evaluated in Part A, the same criteria for determining DLT-evaluable subjects will be applied. Subjects who are non-evaluable for DLT will be replaced. Additional subjects within any dose cohort may be enrolled at the discretion of the SRC. In the event a subject is re-enrolled/re-treated upon relapse (Section 3.1), the subject would only be considered DLT evaluable during the first cycle of their initial enrollment in Part A.

7.2.4 Definition of Non-Tolerated Dose

The NTD is defined as a dose level at which 2 or more of up to 6 evaluable subjects in any dose cohort experience a DLT in Cycle 1 during dose escalation.

If 2 or more of up to 6 subjects experience a DLT in the first dose cohort, a lower dose cohort may be explored at the discretion of the SRC (ie, 0.1 mg CC-90009).

7.2.5 Definition of Maximum Tolerated Dose

The MTD is defined as the last dose level(s) below the NTD with 0 or 1 out of 6 evaluable subjects experiencing a DLT in Cycle 1 during dose escalation. An intermediate dose cohort of CC-90009 (one between the NTD and the last dosing schedule before the NTD) or a variable dose cohort (eg, less frequent dosing) may be evaluated to accurately determine the MTD at the discretion of the SRC.

7.2.6 Definition of Dose-Limiting Toxicity

During dose escalation, the DLT assessment period is Cycle 1 (at least 28 days and up to 42 days).

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 are used as a guide for the grading of severity of adverse events.

A DLT is defined as any of the following toxicities occurring within the DLT assessment unless the event can clearly be determined to be unrelated to CC-90009. Dose-limiting toxicities are described below:

- Any non-hematologic toxicity Grade ≥ 3 EXCEPT for:
  - Grade ≥ 3 nausea, vomiting, dehydration, or diarrhea that responds to standard of care.
  - Grade ≥ 3 fatigue which resolves to Grade ≤ 2 within 7 days (with optimal medical management).
  - Grade ≥ 3 infection.
  - Grade 3 TLS, if controlled by medical management.
  - Grade 3 electrolyte abnormalities other than hypocalcemia (see below) correctable with supportive therapy.
  - Grade 3 laboratory evidence of hypocalcemia of < 24 hours duration in the absence of Grade ≥ 3 clinical symptoms of hypocalcemia.
  - Grade ≥ 3 AST or ALT elevation lasting ≤ 7 days.
    - NOTE: any Grade ≥ 3 AST or ALT in the setting of bilirubin elevation > 2xULN (> 2x baseline for subjects with Gilbert's syndrome) will be a DLT.
- Hematological toxicities as follows:
  - Prolonged myelosuppression, ie, marrow cellularity < 5% or persistent Grade ≥ 3 neutropenia at Cycle 1 Day 42 in the absence of leukemia.
- Any AE, unless clearly determined to be unrelated to the drug, and necessitating dose-level reduction during Cycle 1.

Isolated laboratory changes without associated clinical signs or symptoms (eg, hypomagnesemia, hypermagnesemia, hypoalbuminemia, hypophosphatemia, and lymphocyte count increased or decreased) may not be included in this definition. These findings will be discussed and reviewed by the SRC.

7.2.7 Criteria for Dose Escalation in the Next Cohort of Subjects

Upon completion of the accelerated phase (eg, at least 1 subject in each cohort), cohorts will consist of up to 6 evaluable subjects. The SRC will make dose escalation decisions. The decision criteria for dose escalation are:

- If no more than 0 of 3 or 1 of 6 evaluable subjects experience DLT within the DLT window in a dose cohort, dose escalation to the next higher dose cohort may occur. Additional subjects will be enrolled to expand the cohort to 6 evaluable subjects if less than 6 subjects are evaluable when the DLT is observed.
- If 2 or more of up to 6 evaluable subjects experience a DLT within the DLT window in a dose cohort, any further recruitment will cease and this dose will be defined as the NTD.
- SRC will determine if additional subjects will be enrolled at lower dose cohorts to have 6 evaluable subjects in order to define MTD, or whether an intermediate dose cohort or alternative schedule will be explored in up to 6 newly enrolled subjects.

The number of cohorts depends on incidence of DLT. A subject may experience more than one DLT. Dose escalation decisions are based on the number of subjects experiencing DLT events.

7.2.8 Definition of Stopping Criteria

During Part A, dose escalation stops when ≥ 2 of up to 6 evaluable subjects in any dose cohort experience DLT during the DLT window.

During Part B, non-binding Bayesian stopping rules will be used to continuously monitor for excess toxicity defined as the occurrence of AEs during any cycle that would fulfill the DLT criteria specified in Part A or AEs leading to dose reduction or treatment discontinuation or AEs of sepsis. Details regarding the stopping rules are described in Section 9.9.3.

The SRC will convene regularly to review all the available safety, PK, PD, and efficacy data as well as the results of the Bayesian analysis of excess toxicity and in the event of the following:

- Bayesian stopping criteria are met.
- Unanticipated SAEs that are related to study treatment are reported.
- Death attributable to study treatment is reported.
- The sponsor or IRB/EC decides that subject safety may be compromised by continuing the study.

Decisions to stop the enrollment or terminate the study will be communicated promptly to investigators, to the Institutional Review Boards (IRBs)/Ethics Committees (ECs), Institutional Biosafety Committees ([IBCs], if applicable), and to the appropriate regulatory authorities.

7.2.9 Permitted Study Drug Adjustments

Dose reductions are permitted in any cycle, including Cycle 1. Dose reductions that occur in Cycle 1 during dose escalation will constitute DLT as outlined in Section 7.2.6, but subjects will be allowed to continue on CC-90009 at a reduced dose.

When a dose reduction is indicated, the CC-90009 dose from the next lower dose cohort will be selected or a less frequent dosing schedule after discussion with the Medical Monitor. Subjects will dose reduce using the same formulation to which they are currently assigned (eg, Gen 1 CC-90009 → Gen 1 CC-90009 and Gen 2b CC-90009 → Gen 2b CC-90009). Two dose reductions are allowed. Once the dose has been reduced, it can be escalated when toxicity reaches Grade ≤ 1. If toxicity recurs at the higher dose, the dose will be reduced a second time, but no re-escalation is then permitted. If any subject continues to experience unacceptable toxicity after two dose reductions (one for the starting dose), CC-90009 will be discontinued permanently.

Intra-subject dose escalation of CC-90009 is not permitted during Cycle 1, but escalation to a dose subsequently deemed to be tolerated in a higher dosing cohort may be permitted in later cycles if approved by the SRC.

7.2.10 Criteria for Dose Reduction

Any AE meeting the definition of DLT will require dose reduction and/or interruption. Doses should be delayed if any Grade ≥ 2 toxicities are not resolved to Grade ≤ 1 or baseline by the time of the next dose. Chronic Grade 2 toxicity may warrant dose reduction of CC-90009. Such cases should be discussed with the Sponsor before dosing changes are made. Dose reductions should maintain the subject's current CC-90009 formulation.

7.2.11 Criteria for Dose Increase

In Part A (escalation phase), intra-subject dose escalation beyond the doses initially assigned to a subject is not permitted in Cycle 1. Those continuing to take CC-90009 beyond Cycle 1 may, following approval by the SRC, have the dose increased providing the alternative dose has been shown to be well tolerated by at least one cohort of subjects in this study.

In Part B (expansion phase), no dose escalation beyond the MTD is allowed.

7.2.12 Treatment Interruption/Delay for Adverse Events

In Cycle 1, all CC-90009 doses must be completed on or before Day 10 for the Days 1-5 and Days 1-7 schedule and Day 14 for a Days 1-10 dose schedule (80% of the total planned Cycle 1 dose, eg, ≥ 4 doses for a Days 1-5, ≥ 6 doses for a Days 1-7, or ≥ 8 doses for a Days 1-10 dosing schedule in order to be evaluable for DLT during dose escalation). On the alternate D1-3/D8-10 schedule, doses must be completed on or before the end of Day 14; 80% of the planned total Cycle 1 dose, ≥ 5 doses in order to be evaluable for DLT during Part A).

If CC-90009 dosing is interrupted/delayed during the dosing days of Cycles ≥ 2, the doses of CC-90009 may still be completed within the first 14 calendar days of that cycle. Dosing delays beyond Day 14 of Cycles ≥ 2 will require resuming CC-90009 dosing in the next cycle (if planned).

Treatment cycles with CC-90009 may be interrupted up to 8 weeks until toxicity reaches either Grade ≤ 1 or baseline levels.

Treatment may restart either at the same, or a reduced dose, at the Investigator's discretion or as described in Section 7.2.9. Any such treatment interruptions/delays must be discussed with the Sponsor medical monitor.

7.2.13 Management of Select Adverse Events

7.2.13.1 Prophylaxis and Management of Tumor Lysis Syndrome

Treatment with cytolytic cancer therapies in the setting of high tumor burden may cause rapid tumor lysis and associated electrolyte and renal disturbance with risk of cardiac arrhythmia and sudden death.

Tumor lysis syndrome (TLS) is manifested by rapid release of large amounts of potassium, phosphate and nucleic acids into the circulation with associated hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia. Precipitation of uric acid and calcium phosphate crystals in the renal tubules can result in acute kidney injury and electrolyte disturbances can trigger cardiac arrhythmias, seizures and sudden death.

The risk of TLS with CC-90009 is unknown. As a pre-emptive measure, subjects will be monitored closely for TLS following the administration of each dose of CC-90009. Subjects should be admitted as inpatients during dosing in Cycle 1 and either admitted as inpatients (Investigator's discretion) or monitored in a LSU during dosing days of Cycle ≥ 2. Subjects should be adequately hydrated (eg, 2 to 3 liters of oral or IV fluids per day) starting the day prior to CC-90009 administration and continuing through each day of CC-90009 administration. Medications to prevent or treat TLS are permitted. Medications may include hypouricemic agents (eg, allopurinol, rasburicase), diuretics, and phosphate and potassium binders. Rasburicase is contraindicated in subjects with baseline G6PD deficiency.

Subjects with laboratory abnormalities suspicious for TLS should be managed with hypouricemic agents (eg, allopurinol or rasburicase), intravenous hydration and diuretics as necessary to maintain urine output, and correction of hyperkalemia and hyperphosphatemia, according to standard medical practice (refer to Appendix I). Subjects with laboratory abnormalities suspicious for clinically significant TLS should be managed as inpatients.

7.2.13.2 Hypocalcemia

Alterations in serum chemistry parameters in the cynomolgus monkey studies included decreased serum protein, albumin, and calcium. Subjects will start calcium, calcitriol, and vitamin D supplements at least 3 days prior to starting CC-90009 and continue until ≥ 3 days after the last dose of CC-90009 in each cycle. Guidelines for the management of hypocalcemia are presented in Table 11. If Grade ≥ 2 hypocalcemia or symptoms of hypocalcemia (eg, carpopedal spasm, tetany, seizures, etc) occur, the subject must be hospitalized. Also, if Grade ≥ 2 hypocalcemia and abnormal levels of serum albumin occurs, a serum ionized calcium test must be performed. If Grade ≥ 3 hypocalcemia persists for greater than 24 hours despite medical management or if any Grade ≥ 3 symptoms of hypocalcemia occur, study drug will be held until the hypocalcemia resolves to Grade ≤ 1. Study drug should be restarted at the next lower dose.

If Grade ≥ 2 hypocalcemia occurs in any cycle, subjects should be admitted as inpatients for the administration of CC-90009 during subsequent cycles (an exception can be made for subjects with grade 2 hypocalcemia lasting less than 24 hours that recovers without IV calcium [eg, calcium gluconate or calcium chloride] after discussion with the Celgene medical monitor). For these subjects, additional calcium monitoring on dosing days (eg, Days 1-5, Days 1-7, or Days 1-10) at 6 and 12 hours (± 1 hour) postdose should be performed during Cycle ≥ 2.

Table 11: Management of Hypocalcemia

	Corrected Serum Total Calcium[a]			
	Grade ≤ 1	**Grade 2**		**Grade ≥ 3**
	≥ 8.0 mg/dL (≥ 2.0 mmol/L) (ionized ≥ 1.0 mmol/L)	**< 8.0 – 7.5 mg/dL (< 2.0 – 1.88 mmol/L) (ionized < 1.0 – 0.95 mmol/L)**	**< 7.5 – 7.0 mg/dL (< 1.88 – 1.75 mmol/L) (ionized < 0.95 – 0.9 mmol/L)**	**< 7.0 mg/dL (< 1.75 mmol/L) (ionized < 0.9 mmol/L)**
Hospitalization for monitoring	Not required	Monitor calcium as inpatient Q6 hours or as clinically indicated until trending upward[b]	Monitor calcium as inpatient Q6 hours or as clinically indicated until trending upward[b]	Monitor calcium as inpatient Q6 hours or as clinically indicated until trending upward[b]
IV calcium gluconate[c]	Not required	Administer as needed for acute symptomsd or prolonged QT	Administer as needed for acute symptoms[d] or prolonged QT (consider in absence of symptoms if rapid decrease)	Administer as needed for acute symptoms[d] or prolonged QT (consider in absence of symptoms if rapid decrease)
Oral calcium	1200-1500 mg of elemental calcium per day in divided doses	1200-1500 mg of elemental calcium per day in divided doses	2400-2500 mg of elemental calcium per day in divided doses	2400-2500 mg of elemental calcium per day in divided doses
Vitamin D therapy	calcitriol 0.25 µg QD	calcitriol 0.25 µg BID	calcitriol 0.5 µg BID	calcitriol 0.5 µg BID

AC = before meals; BID = twice a day; IV = intravenous; PO = by mouth; TID = three times a day.

a Corrected Ca (mg/dL) = Total Ca (mg/dL) – 0.8 [albumin (g/dL) – 4].

b Also check for concurrent hypomagnesemia and correct with supplementation if present.

c One to 2 g of calcium gluconate (= 90-180 mg elemental calcium), in 50 mL of saline infused over 10-20 min. This dose of calcium gluconate will raise the serum calcium for only 2-3 hours. It should be followed by a slow infusion of calcium in patients with persistent hypocalcemia.

d For example, carpopedal spasms, tetany, seizures, etc.

7.2.13.3 Neutropenia and Anemia

Hematopoietic growth factors or other hematologic support, such as erythropoietin, darbepoetin, granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor, RBC- or platelet- transfusions are allowed in the study with therapeutic intent. Therapeutic use of G-CSF is allowed at any time for subjects experiencing Grade 3/4 neutropenia or any grade febrile neutropenia. Prophylactic use of granulocyte (or granulocyte-macrophage) growth factors is not allowed during Cycle 1.

Subjects with Grade 3 or 4 neutropenia should be monitored frequently with laboratory tests until resolution to Grade ≤ 1. Antimicrobial, antifungal, and antiviral prophylaxis should be considered and provided per institutional standard medical practice.

7.2.13.4 Infection

Vigilance for the signs and symptoms of infection should be practiced and managed according to institutional standard medical practice. Routine infectious disease prophylaxis including appropriate prophylactic antibiotic, antiviral, antipneumocystis, antifungal, or other prophylaxis should be implemented during the study according to institutional standard medical practice.

7.2.13.4.1 SARS-CoV-2 Infection

Subjects with confirmed SARS-CoV-2 infection following the start of CC-90009 administration must have treatment interrupted.

For confirmed SARS-CoV-2 infection, treatment may be resumed after:

1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared, positive RT-PCR test result, or positive viral antigen test result,
2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications),
3) evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, and
4) consultation by the Sponsor Medical Monitor.

For suspected cases, treatment may resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met. Prior to re-initiating on-study treatment in a subject with a dosing delay lasting more than 8 weeks due to SARS-CoV-2 infection, the Medical Monitor/designee must be consulted.

7.2.13.5 Pain

Tumor pain or treatment-induced pain can be controlled with opioid and opioid-related analgesics, such as codeine, meperidine, propoxyphene or morphine, administered at the clinician's discretion, and as dictated by medical need. The risk of bleeding, especially in the setting of thrombocytopenia, should be considered prior to use of non-steroidal anti-inflammatory drugs and aspirin.

7.2.13.6 Diarrhea

It is recommended that subjects experiencing diarrhea be managed according to the guideline provided in Appendix J. Antidiarrheal medication may be administered as prophylaxis and for treatment of diarrhea.

7.2.13.7 Infusion Reactions

Infusion of a chemotherapeutic product may cause infusion reactions ranging from localized injection site reactions to severe and life-threatening reactions. Infusion reactions may occur with the first or subsequent infusions and typically develop within 24 hours of infusion (Vogel, 2010).

Symptoms may include hypotension, tachycardia, dyspnea and respiratory symptoms (eg, bronchospasm, throat irritation, wheezing, and laryngeal edema). Other possible symptoms include nausea, vomiting, diarrhea, hypertension, flushing, skin rash, urticaria, headache, fever and chills. Full emergency resuscitation facilities should be immediately available and subjects should be under close supervision of the Investigator or appropriately trained staff during administration of CC-90009 and for at least 1 hour after.

Medical management of infusion reactions should be instituted according to standard medical practice using glucocorticoids, epinephrine, oxygen, intravenous fluids and other medications as medically indicated.

7.2.13.8 Hypotension

Grade 2 and 3 hypotension TEAEs have occurred in subjects treated with CC-90009. Hypotension has been typically observed on or within 24 hours of the days of dosing. Standard CC-90009 dose interruption and modification guidance for non-hematologic toxicity Grade 3/4 AEs should be followed (Section 7.2.9).

- Infection should be considered in all subjects presenting with hypotension (with or without fever) and appropriate cultures must be obtained and empiric antibiotic therapy initiated per institution standard of care.
- Grading of hypotension for this protocol has been clarified, as subjects are already hospitalized during days of dosing (Table 12 and Lee, 2014).
- Management of Grade 2 hypotension[a]:
  - IV fluids (eg, initially 500 to 1000 mL or per institutional guidance)
  - Addition of anakinra 100 mg administered by subcutaneous injection (recombinant, nonglycosylated human interleukin-1 receptor antagonist [IL-1Ra]). Anakinra should be administered Q12 hours (or per institutional practice for management of CRS) until resolution of CC-90009-related hypotension
  - Consider adding dexamethasone (eg, 10 mg IV, Q12 hours until resolution or per institutional guidance)
- Management of Grade ≥3 hypotension[a]:
  - If unresponsive to IV fluids and anakinra, consider escalation to higher level of medical care (eg, intensive care unit) and adding single low-dose vasopressor
  - Addition of high-dose or multiple vasopressors if unresponsive to single low-dose vasopressor (Table 13)

[a] The management of Grade ≥ 2 CC-90009 associated hypotension should be as per local institution clinical practice guidelines.

Table 12: Modified Grading for Hypotension for CC-90009

Systolic Blood Pressure (SBP) < 90 mm Hg	Grade 1	Grade 2	Grade 3	Grade 4
Study Specific Grading	Asymptomatic, intervention not indicated	Responds to intravenous (IV) fluids and/or anti-cytokine therapy (eg, anakinra, steroids)	Needs IV vasopressor(s)	Life-threatening

Table 13: High-dose Vasopressors (all doses are required for ≥ 3 hours)

Pressor	Dose
Norepinephrine monotherapy	≥ 20 µg/min
Dopamine monotherapy	≥ 10 µg/kg/min
Phenylephrine monotherapy	≥ 200 µg/min
Epinephrine monotherapy	≥ 10 µg/min
If on vasopressin	Vasopressin + norepinephrine equivalent of ≥10 µg/min*
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥20 µg/min*

Source: Lee, 2014.

* VASST Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (µg/min)/2] + [dopamine (µg/kg/min) / 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) /10].

7.2.14 Definition of Overdose

Overdose, as defined for this protocol, refers to CC-90009 dosing only. On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of CC-90009 assigned to a given subject, regardless of any associated adverse events or sequelae:

- 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form. Refer to Section 10 for the reporting of adverse events associated with overdose.

7.2.15 Dosage Modifications for Concomitant Use of Strong CYP3A4 Inhibitors in Part B Dose Expansion

In Part B, dosage modification of CC-90009 based on concomitant use with a strong CYP3A4 inhibitor (See Section 8.2 for list of example CYP3A4 inhibitors) will be as follows:

- For 3.0 mg Days 1-7 cohort, reduce CC-90009 dose to 2.0 mg
- For 2.4 mg Days 1-7 cohort, reduce CC-90009 dose to 1.5 mg

Resume the CC-90009 dosage that was used prior to concomitant use of a strong CYP3A4 inhibitor 3 days after discontinuation of the inhibitor.

No dose modification is required for concomitant use of moderate CYP3A4 inhibitors.

7.3 Method of Treatment Assignment

Subjects will be enrolled sequentially in Part A with no more than one subject enrolled per day into dose escalation cohorts. Enrollment in Part B will be stratified by disease cohort and dosing schedule, as applicable.

An IRT system will be used to track subject assignments to the dose levels in dose escalation (Part A) and cohorts in dose expansion (Part B).

7.4 Packaging and Labeling

The label(s) for CC-90009 will include sponsor name, address and telephone number, the protocol number, dosage form and strength (where applicable), lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations. Gen 2b material will be clearly labeled as Gen 2b. Labeling for each formulation will be color coded as per the Pharmacy Manual for that formulation.

7.5 Investigational Product Accountability and Disposal

Celgene (or designee) will review with the Investigator and relevant site personnel the process for investigational product return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

7.6 Investigational Product Compliance

Only the pharmacist or the Investigator's designee will dispense CC-90009. A record of the total dose (and number of vials used) of CC-90009 administered to each subject must be maintained.

The pharmacist or Investigator's designee will document the doses dispensed/administered in the appropriate study records and the appropriate eCRF.

8 CONCOMITANT MEDICATIONS AND PROCEDURES

All medications (excluding prior cancer therapy for the tumor under evaluation) taken beginning when the subject signs the ICD and all concomitant therapy during the study until 28 days after treatment discontinuation, together with dose, dose frequency and reasons for therapy use will be documented in the source documents and on the concomitant medication eCRF.

All prior cancer therapy for the tumor under evaluation, including chemotherapy, biologic, immunologic, irradiation, and surgery, will be documented on dedicated prior cancer treatment eCRFs.

The Investigator will instruct subjects to notify the study staff about any new medications taken after signing the ICD. All medications and significant non-drug therapies (herbal medicines, physical therapy, etc.) and any changes in dosing with existing medications will be documented on the eCRFs.

8.1 Permitted Concomitant Medications and Procedures

Subject to the precautions described in Section 8.2, the use of any concomitant medication/therapies deemed necessary for the care of the subject should be used. Repeat PK evaluations may be conducted if changes are made to concomitant medications suspected of affecting drug absorption or metabolism.

Medications to prevent or treat TLS are permitted. Medications may include hypouricemic agents (eg, allopurinol, rasburicase), diuretics, and phosphate and potassium binders. Rasburicase is contraindicated in subjects with screening G6PD deficiency.

Medications to treat infusion reactions are permitted. Medications may include antihistamines, H2-blockers, anti-pyretics, corticosteroids, bronchodilators and other medications as medically indicated.

Routine prophylaxis with granulocyte colony stimulating factor or granulocyte-macrophage colony stimulating factor is allowed at the Investigator's discretion after Cycle 1.

Subjects receiving recombinant erythropoietin or darbepoetin alfa for at least 4 weeks prior to starting the CC-90009 may continue their pretreatment doses throughout the study.

Leukapheresis to control leukocytosis is permitted unless it is within the 2 weeks prior to the first dose of CC-90009. In Cycles 1-4, leukapheresis cannot be performed the same day as CC-90009 dosing.

Hydroxyurea to control leukocytosis is permitted during screening and Cycle 1 at the Investigator's discretion.

Parenteral flu vaccination is permitted.

Routine infectious disease prophylaxis including appropriate prophylactic antibiotic, antiviral, antipneumocystis, antifungal, or other prophylaxis should be implemented during the study according to institutional standard medical practice.

Subjects may receive approved or authorized COVID-19 vaccines while continuing on study treatment at the discretion of the Investigator. COVID-19 vaccines that are NOT live are allowed and should be handled in the same manner as other vaccines. Administration may occur during the study, including during the administration of the BMS study treatment and after the last administration of the BMS study treatment.

Treatment of active SARS-CoV-2 infections or high risk exposures, including use of investigational therapies, is allowed and should be discussed with the Sponsor Medical Monitor.

Even though CC-90009 is not anticipated to cause drug interactions when administered with CYP2C9 and CYP2C19 substrates at clinically relevant concentrations, caution should be used with narrow therapeutic index substrates such as warfarin, clopidogrel, voriconazole, phenytoin, fluindione and acenocoumarol, consistent with general clinical practice.

8.2 Prohibited Concomitant Medications and Procedures

Other investigational therapies must not be used while the subject is on the study.

Anticancer therapy (chemotherapy, biologic or investigational therapy, and surgery), other than the study treatments and hydroxyurea during Cycle 1, must not be given to subjects while the subject is on the study. If such treatment is required the subject must be discontinued from the study. Focal palliative radiotherapy for treatment of cancer-related symptoms is allowed during study treatment at the discretion of the Investigator. Maintenance hormonal therapies are allowed in subjects with a history of breast or prostate cancer.

Treatment with chronic, therapeutic dosing of anti-coagulants (eg, warfarin, low molecular weight heparin, Factor Xa inhibitors) should be used with caution based on an overall risk-benefit assessment. Short-term, prophylactic dosing of anticoagulants may be considered in subjects if medically indicated (eg, hospitalized patients, post-operatively).

Administration of investigational (not approved or authorized by relevant health authorities) COVID-19 vaccines is not allowed during the study. Live COVID-19 vaccines should not be administered to a subject during the study, including during the treatment, safety follow-up period and within 3 months following the last dose of study drug. In addition, the administration of a live COVID-19 vaccine is prohibited at least 14 days prior to initiation of study treatment.

Concomitant use with a strong CYP3A4 inhibitor increases CC-90009 exposure, which may increase CC-90009 toxicities, including the risk of sepsis. Avoid concomitant use of CC-90009 with strong CYP3A4 inhibitors if possible. Alternative treatments for anti-fungal prophylaxis or medication (eg, micafungin, caspofungin, or amphotericin) should be considered. If concomitant use of strong CYP3A4 inhibitors is unavoidable during study treatment, CC-90009 dose reductions are required (Section 7.2.15) and subjects should be monitored closely for signs of toxicities. Subjects can resume CC-90009 at the dose used prior to initiation of the concomitant strong CYP3A4 inhibitor 3 days after discontinuation of the inhibitor.

- Examples of strong CYP3A4 inhibiting medications: Atazanavir, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, darunavir, elvitegravir/ritonavir, indinavir, itraconazole, ketoconazole, lonafarnib, lopinavir/ritonavir, mibefradil, mifepristone,

nefazodone, nelfinavir, paritaprevir/ritonavir combinations, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole

Concomitant use with a strong or moderate CYP3A4 inducer may decrease CC-90009 efficacy. Avoid concomitant use of CC-90009 with strong or moderate CYP3A4 inducers. Alternative treatments with less CYP3A4 induction should be considered.

- Strong CYP3A4 inducers: avasimibe, carbamazepine (Tegretol®), enzalutamine, mitotane, phenytoin (Dilantin®), rifampin (Rifadin®), St. John's wort
- Moderate CYP3A4 inducers: bosentan, efavirenz, etravirine, modafinil, nafcillin

8.3 Required Concomitant Medications and Procedures

All subjects will be required to start calcium, calcitriol, and vitamin D supplementation at least 3 days prior to the first dose of CC-90009 in each cycle and continue until ≥ 3 days after the last dose of CC-90009 in each cycle. Supplementation may be extended if hypocalcemia occurs (refer to Section 7.2.13.2). Subjects will document (date and time) taking the supplements on diary cards that will be reviewed on Day 1 of each cycle and at the EOT visit.

The calcium/calcitriol/vitamin D supplementation regimen is:

- Calcium carbonate 500 mg elemental calcium PO 3 TID (taken after meals to increase absorption)
  - Alternative preparations of calcium can be substituted but they must equal at least 1200 mg of elemental calcium per day given in divided doses (eg, TID).
  - If the subject is on a proton pump inhibitor (PPI) or has gastric achlorhydria, then administer calcium citrate 630 mg elemental calcium PO TID or closest higher dose based on available strengths.
- Calcitriol 0.25 micrograms PO QD
- Vitamin D supplementation is based on the Screening serum 25-hydroxyvitamin D level:
  - Level < 12 ng/mL – excluded from the study
  - Level 12 – 20 ng/mL – Vitamin D3 or D2 50,000 IU weekly
  - Level > 20 ng/mL– Vitamin D3 or D2 1000 IU QD

The risk of TLS with CC-90009 is unknown. Subjects should be adequately hydrated (eg, 2 to 3 liters of oral or IV fluids per day) starting the day prior to CC-90009 administration and continuing through each day of CC-90009 administration.

Subjects given CC-90009 at daily doses ≥ 3.6 mg will be administered concurrent dexamethasone per Section 7.2. Subjects enrolled on other dose levels may be administered corticosteroid premedication as per SRC recommendation (eg, at the 3.0 mg dose level on the Days 1-7 and Days 1-10 schedules).

Routine infectious disease prophylaxis including appropriate prophylactic antibiotic, antiviral, anti-pneumocystis, antifungal, or other prophylaxis should be implemented during the study according to institutional standard medical practice.

9 STATISTICAL CONSIDERATIONS

9.1 Overview

The primary objectives of this Phase 1 study are to determine the safety and tolerability of CC-90009, and to define the NTD, MTD, and/or the RP2D of CC-90009. The secondary objectives are to provide information on the preliminary efficacy of CC-90009 in R/R AML and R/R HR-MDS, and to characterize the PK of CC-90009 in plasma and urine.

Data summaries/statistical analyses will be performed by study phase, dose level/dosing regimen and cohort as needed or applicable in the dose escalation phase (Part A) and dose expansion phase (Part B) separately, as well as at dosing regimen(s) used for expansion that include the subjects from both study phases. For retreated subjects, the safety data collected during the initial and the retreated period will be combined for the analysis. The efficacy data will be analyzed and reported for the initial treatment period only.

9.2 Study Population Definitions

The study population definitions are as follows:

- Enrolled Population – All subjects who meet all the inclusion/exclusion criteria and are eligible for the study.
- Treated Population – All subjects who enroll and receive at least one dose of CC-90009.
- Efficacy Evaluable (EE) Population – All subjects who enroll in the study, meet eligibility criteria, complete at least one cycle treatment or receive at least 80% of scheduled dose in Cycle 1, have a baseline leukemia assessment evaluation and at least one valid post-baseline leukemia assessment.
- Pharmacokinetic (PK) Evaluable Population – all subjects who enroll and receive at least one dose of CC-90009 and have at least one measurable concentration of CC-90009.
- Biomarker Evaluable (BE) Population – all subjects who enroll, receive at least one dose of study drug, and have at least one biomarker assessment, excluding disqualified assessments.

9.3 Sample Size and Power Considerations

During Part A (dose escalation) of the study, a modified accelerated titration design (Simon, 1997) will be used for dose escalation as described in Section 7.2. The total number of subjects in Part 1 will depend on the number of dose escalations required to reach the NTD and cannot be determined in advance. However, the anticipated number of subjects will be approximately 40 to 60.

Following completion of dose escalation (Part A), one or more dosing regimens may be selected with up to approximately 20 evaluable subjects each for R/R AML or R/R HR-MDS at each selected dosing regimen for an expansion phase (Part B). Expansion may occur at the MTD and schedule established in the dose escalation phase, and/or at an alternative tolerable dose and schedule, based on review of safety, PK, and PD data from Part A. Sample sizes are not determined based on power calculation but rather on clinical, empirical and practical considerations traditionally used for exploratory studies of this kind.

At least 13 efficacy evaluable subjects with R/R AML in Part B will be accrued. If the response rate is 30% or more, the probability of seeing no response in the first 13 R/R AML subjects will be less than 1% (Gehan, 1961). If no response is observed out of 13 R/R AML subjects, the enrollment for this cohort will stop for futility. Otherwise, the enrollment will be expanded to up to approximately 20 evaluable subjects each for R/R AML or R/R HR-MDS for this cohort. The 2-sided 95% confidence interval for 20% and 30% response rate is tabulated in Table 14 for different sample size scenarios.

Table 14: Confidence Interval for 20% and 30% Response Rate for Different Scenarios of Sample Size (Wilson score interval)

CI	Response rate	Sample size			
		13	20	30	40
0.95	0.2	(0.066 ,0.471)	(0.081 ,0.416)	(0.095 ,0.373)	(0.105 ,0.348)
0.95	0.3	(0.122 ,0.569)	(0.145 ,0.519)	(0.167 ,0.479)	(0.181 ,0.454)

CI = confidence interval.
Source: Gehan, 1961.

9.4 Background and Demographic Characteristics

Subjects' age, weight, height and other continuous demographic and baseline variables will be summarized using descriptive statistics. Gender, race and other categorical variables will be summarized with frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term. Prior therapies will be summarized by frequency tabulation, if available. Supportive corresponding subject listings will also be provided.

9.5 Subject Disposition

Subject disposition (analysis population allocation, on-going, discontinued from treatment and/or study, along with primary reason for discontinuation) will be summarized using frequency and percent. A summary of subjects enrolled by site will be provided. Protocol violations will be summarized using frequency tabulations. Supportive corresponding subject listings will also be provided.

9.6 Efficacy Analysis

Efficacy analyses will be based on the Treated Population and certain efficacy analyses will also be performed on the EE Population. Leukemia response will be determined by the Investigator based on the IWG Response Criteria in AML (Cheson, 2003; refer to Appendix C). MDS response will be based on the IWG Response Criteria for Myelodysplasia (Cheson, 2006; refer to Appendix G). Efficacy endpoints include complete remission rate (CRR), objective response rate (ORR), and time-to-event efficacy variables.

9.6.1 Complete Remission Rate and Objective Response Rate

The CRR is defined as the rate for any type of CR. The ORR is defined as the rate for all response categories, including all types of CRs, MLFS, and PR for AML. For MDS, the ORR includes all

responses (CR, mCR and PR). The efficacy variable of focus will be ORR and CRR. Other measures of clinical activity including overall survival (OS), relapse-free survival (RFS), progression-free survival (PFS), event-free survival, duration of remission, duration of response, time to transformation to AML (HR-MDS subjects only) and time to remission/response will be summarized. Overall response rate and CRR will be summarized using frequency tabulation. Two-sided 95% Clopper-Pearson exact confidence intervals (Clopper, 1934) will be provided for ORR and CRR estimates.

9.6.2 Time to Event Variables

Other measures of clinical activity including overall survival (OS), relapse-free survival (RFS), progression-free survival (PFS), event-free survival, duration of remission, duration of response and time to remission/response will be summarized. Subjects who have completed the treatment phase without documented progression of disease will have efficacy evaluations performed as specified in Section 6.3.2. Subjects will be followed for overall survival as specified in Section 6.3.3.

The Kaplan-Meier estimate of the median of RFS, PFS, and OS along with their 95% confidence interval will be provided (Brookmeyer, 1982). The RFS, PFS, and OS rates at selected time points will be computed using the Kaplan-Meier estimates, along with standard errors of rate (Greenwood's formula, Klein, 2003). Duration of remission/response and time to remission/response will also be reported in subjects who achieve remission/response, using tumor specific evaluation criteria.

MDS cohort in Part B

For the HR-MDS cohort, transformation to AML and time to transformation to AML will be summarized.

Listings and graphical displays will be provided where useful for the interpretation of results.

Full details on the efficacy analysis are described in the Statistical Analysis Plan (SAP).

9.7 Safety Analysis

Adverse events, including treatment-emergent adverse events (TEAEs), laboratory assessments, vital signs, ECG results, ECOG performance status, LVEF assessments, physical examinations, vital signs, exposure to study treatment, assessment of concomitant medications, and pregnancy testing for females of child bearing potential will be summarized for the Treated Population.

Adverse events observed will be classified using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of the toxicities will be graded according to the NCI CTCAE (Version 4.03) whenever possible. The frequencies of adverse events will be tabulated by MedDRA (Version 17.1 or higher) System Organ Class and Preferred Term. In the by-subject analysis, a subject having the same AE more than once will be counted only once. Adverse events will also be summarized by NCI CTCAE grade. Adverse events leading to dose reduction/interruption or permanent discontinuation of study treatment, events classified as CTCAE Grade 3 or 4, study drug-related AEs, deaths, and SAEs will be tabulated. By-subject listings of all AEs, deaths, and SAEs and their attribution will be provided.

Clinical laboratory results will be summarized descriptively, which will include a display of change from baseline. Bidirectional shift tables (low and high) demonstrating the change of CTCAE grades from baseline to the worst post-baseline severity grade during the treatment period will also be presented for applicable tests. Listings of abnormal clinical laboratory data according to NCI CTCAE severity grades (if applicable), abnormal flags (low or high) and clinical significance of the latter will be provided. Graphical displays (eg, "spaghetti" plots or box plots) will be provided for key laboratory tests.

Descriptive statistics for ECG, vital sign and LVEF measurement, both observed values and changes from baseline, will be summarized. Shift tables demonstrating the changes from baseline to the worst post-baseline qualitative assessment of abnormality will be displayed in cross-tabulations. Post-baseline abnormal ECG and LVEF values will be summarized using frequency tabulations. ECG, vital sign and LVEF measurements will be listed by subject.

Graphical displays will be provided where useful in the interpretation of results.

9.8 Interim Analysis

No formal interim analysis is planned. Data will be reviewed on an ongoing basis.

9.9 Other Topics

9.9.1 Assessment of Pharmacokinetics

Noncompartmental plasma PK parameters of CC-90009, such as C_{max}, AUC_{24}, CL, Vss, and $t_{1/2}$, will be estimated and summarized by dose level and visit, when feasible. Selected plasma PK parameters (eg, C_{max}, AUC_{24}, and $t_{1/2}$,) will be estimated and summarized for the R- and S-enantiomers of CC-90009, respectively. Urine PK parameters of CC-90009, such as F_e and CL_R, will be estimated and summarized for the RP2D. Main plasma and urine PK parameters as described above will also be estimated for hydroxypropyl-β-cyclodextrin at the RP2D. Other PK parameters may be calculated as appropriate.

Descriptive statistics (number of subjects [N], mean, standard deviation [SD], coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum, and maximum) will be provided for drug concentration data and PK parameters. Results will be presented in tabular and/or graphic forms as appropriate.

A population PK analysis for CC-90009 may be conducted using both intensive and sparse PK samples to explore the inter-individual variability of plasma drug exposure and the contributing factors (covariates). The relationship between CC-90009 doses, plasma exposures, and selected clinical endpoints (eg, measures of toxicities, effectiveness, and/or biomarkers) may be explored as appropriate. The population PK model, in combination with the knowledge on exposure-response, may be used to explore dosing regimens for Part B or phase 2 studies.

9.9.2 Assessment of Pharmacodynamics

Descriptive statistics (N, mean, standard deviation, median, min, and max) will be provided for baseline, post-baseline values, and changes from baseline or percent change from baseline of each biomarker. Subjects' biomarker results changing over time will be plotted. Comparison of

biomarker levels before and during treatment will be performed by Wilcoxon signed rank test. If sufficient and valid results from biomarker assays can be obtained, the relationship between biomarker levels and PK or clinical endpoints including CRR, ORR and time-to-event variables will be explored.

9.9.3 Stopping Rules Regarding Toxicity in Part B Dose Expansion

During dose expansion phase (Part B), a non-binding Bayesian method will be utilized to monitor excess toxicities defined as the occurrence of AEs during any cycle that would fulfill the DLT criteria specified in Part A or treatment related AEs leading to dose reduction or discontinuation or the occurrence of sepsis. The enrollment in the corresponding expansion cohort will pause to ensure the posterior probability of excess toxicity rate exceeding 25% is not more than 70%, ie, when

Prob (rate of AEs that fulfill the DLT criteria or treatment-related AEs leading to dose reduction or discontinuation or rate of sepsis >0.25|data, a, b) > 0.7.

Where a, b are parameters of Beta distribution. Weakly informative priors, ie, Beta (0.5, 0.5), may be used to calculate the posterior probability. The excess toxicity rate of 25% is established based on clinical inputs with threshold of 70% based on empirical data analysis.

After a minimum of 8 subjects have enrolled and taken at least one cycle of study treatment for a cohort, the posterior distributions of excess toxicity will be calculated on a continuous basis for every subject enrolled (Table 15).

The operating characteristics of the proposed Bayesian safety monitoring plan are detailed in Appendix P.

Table 15: Stop Boundaries Based on Stopping Criteria for Each Expansion Cohort

Number of Subjects	Number of Subjects with AEs fulfilling DLT or other criteria that would prompt potential enrollment pause
8	3
10	4
13	5
17	6
21	7
24	8
28	9
32	10
35	11
39	12

AE = adverse event; DLT = dose limiting toxicity

Note: Only unique stopping boundaries are presented up to the estimated maximum enrollment of 40 subjects in an expansion cohort.

The SRC will convene regularly (eg, monthly) to review the overall safety/tolerability data and to assess the Bayesian analysis output. Each subject that experiences an AE that meets the above criteria will be reviewed by the SRC, and the overall Bayesian Analysis will be run at that time to guide the SRC on cohort decisions. If the stopping rule is triggered, the SRC will conduct a comprehensive review of available safety, PK, PD, and preliminary efficacy data to make continuation decisions. Decisions to pause enrollment of specific expansion cohort(s) or terminate the study will be determined by the SRC and communicated properly to Investigators, IRBs, and appropriate regulatory authorities.

10 ADVERSE EVENTS

10.1 Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose eCRF (refer to Section 7.2.14 for the definition of overdose). Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for CC-90009 overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of CC-90009 as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to CC-90009. AEs and SAEs will be recorded in the eCRF and in the subject's source documents. Refer to Section 10.5 for instructions on how to report SAEs to Celgene Drug Safety.

Subjects will be followed for all SAEs, and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the subject is lost to follow-up, or for suspected cases, until SARS-CoV-2 infection is ruled-out.

10.2 Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1 Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to the IP, action taken regarding the IP, and outcome.

10.2.2 Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/ intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the CTCAE, Version 4.03; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death – the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3 Causality

The Investigator must determine the relationship between the administration of the CC-90009 and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: a causal relationship of the adverse event to CC-90009 administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: there is a **reasonable possibility** that the administration of CC-90009 caused the adverse event. 'Reasonable possibility'

means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional CC-90009 that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4 Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

10.2.5 Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6 Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.3 Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of CC-90009 dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4 Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or partner of childbearing potential of a male subject are immediately reportable events.

In the event of a pregnancy occurring in a female subject of childbearing potential or female partner of a male subject, Celgene will follow up with the clinical investigator each trimester of pregnancy and for 1 year following the birth of the infant (if applicable). Please reference the pregnancy information consent (permission) forms for data collection for additional information.

The exposure of any pregnant female (eg, caregiver, pharmacist, study coordinator or monitor) to CC-90009 is also an immediately reportable event.

10.4.1 Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on CC-90009, or within 28 days of the subject's last dose of CC-90009, are considered immediately reportable events. Investigational product is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling. The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the CC-90009 should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.4.2 Male Subjects

If a female partner of a male subject taking CC-90009 becomes pregnant, the male subject taking CC-90009 should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. Where applicable, the CC-90009 may need to be discontinued in the male subject, but may be resumed later at the discretion of the Investigator and medical monitor.

10.5 Reporting of Serious Adverse Events

Any AE that meets any serious criterion requires reporting as an SAE within 24 hours of the Investigator's knowledge of the event. This instruction pertains to initial SAE reports as well as any follow-up reports.

This requirement applies to all SAEs (regardless of relationship to CC-90009) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of CC-90009) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to CC-90009. Serious adverse events occurring prior to treatment (after signing the ICD) are to be recorded within the CRF, but do not require reporting to Celgene Drug Safety.

The SAE is reported directly to Celgene Drug Safety by facsimile, or other appropriate method using the SAE Report Form or approved equivalent form. The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, results of the autopsy report and/or death certificate are to be reported to Celgene Drug Safety as soon as these become available. Any follow-up data, including responses to safety queries, should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety. Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. Urgent queries (eg, missing causality assessment) may be handled by phone.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

10.6 Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to CC-90009 based on the Investigator Brochure.

In the United States, expedited reports sent to the FDA by the sponsor based on the reasonable possibility threshold are known as 'IND safety reports' and will be reported in accordance with 21 CFR 312.32.

For reporting to the FDA, events that are not suspected to be causally related to CC-90009 by the sponsor will not be considered adverse reactions. As per FDA regulations, events that are anticipated in the study population (refer to Section 7.2.13 and the CC-90009 Investigator's Brochure Section 6.3.8 Reference Safety Information) will not be considered adverse reactions on individual assessment and will be reviewed on an aggregate basis for assessment of frequency.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse

reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of CC-90009 in this study or in other studies that is both serious and unexpected (eg, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 14.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

11 DISCONTINUATIONS

11.1 Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the investigational product:

- Adverse Event
- Withdrawal by subject
- Treatment failure
- Physician decision
- Protocol violation
- Progressive disease
- Death
- Lost to follow-up
- Pregnancy
- Lack of efficacy
- Other (to be specified on the eCRF)

The reason for discontinuation of treatment should be recorded in the eCRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. Subjects with progressive disease who, in the opinion of the Investigator, are deriving clinical benefit may remain on study after discussion with the Medical Monitor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

11.2 Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Withdrawal by subject
- Physician decision
- Protocol violation
- Death
- Lost to follow-up
- Other (to be specified on the eCRF)

The reason for study discontinuation should be recorded in the eCRF and in the source documents.

12 EMERGENCY PROCEDURES

12.1 Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

12.2 Emergency Identification of Investigational Products

This is an open-label study; therefore, CC-90009 will be identified on the package labeling.

Subjects enrolled in this study will be issued an identification card showing the name of this study and an emergency contact number. This can be used by health care professionals seeking emergency information about a subject's participation in the study.

13 REGULATORY CONSIDERATIONS

13.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by GCP, as described in ICH Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2 Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3 Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4 Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5 Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

13.6 Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue

a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

13.7 Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8 Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14 DATA HANDLING AND RECORDKEEPING

14.1 Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of eCRFs or CD-ROM.

14.2 Data Management

Data will be collected via eCRF and entered into the clinical database per Celgene SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3 Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- CC-90009 accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period.

The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

15 QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1 Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the eCRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2 Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

15.3 Investigational Medicinal Product Quality Issues

Issues that call into question IP safety, purity, potency, quality and identity (eg, evidence of suspected tampering of product) must be reported as soon as possible to the study Clinical Trial Monitor and/or Clinical Trial Manager or designee. Report an issue or concern with all sponsor supplied IP suspected to have occurred before the product was transferred to the responsibility of the investigational site (eg, during manufacturing, packaging and labeling, storage, and/or distribution).

This includes suspected quality issues of components co-packaged with the drug, labelling, and IP device/drug combination products, and medical devices.

In the event of a suspected product quality issue, the immediate action to be taken by site is to quarantine the affected product. Do not dispose of the product unless retention presents a risk to personnel (eg, cytotoxic, risk of injury from broken glass or sharps).

When reporting, provide as much product information as possible. Suspected IP quality issues will be investigated and a response will be provided back to the investigational site.

16 PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

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18 APPENDICES

Appendix A: Table of Abbreviations

Table 16: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AC	Before meals
ADL	Activity of daily life
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the plasma concentration-time curve
AUC_t	AUC calculated to the last observable concentration at time t
β-CTx	β-C-terminal telopeptide
β-hCG	β-subunit of human chorionic gonadotropin
BID	Two times a day
BUN	Blood urea nitrogen
C	Cycle
C_{5min}	Plasma concentration at 5 minutes
Ca	Calcium
CBC	Complete blood count
CD	Cluster of differentiation
CEBPα	CCAAT/enhancer binding protein alpha
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed concentration of drug
CNS	Central nervous system
CO2	Carbon dioxide
CR	Complete remission
CRBN	Cereblon
CRc	Cytogenetic complete remission
CRF	Case report form
CRh	Morphologic CR with partial hematologic recovery

Table 16: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
CRi	Morphologic CR with incomplete blood recovery
CRL	Cullin ring ligase
CRm	molecular CR
CRR	Complete remission rate
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of variation
CYP	Cytochrome P450
D	Day
DLT	Dose-limiting toxicity
DMA	N,N,-Dimethylacetamide
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EEA	European Economic Area
EFS	Event-free survival
E_{max}	Maximum possible effect
EMD	Extra medullary disease
EOI	End of injection
EOT	End of treatment
FCBP	Females of child bearing potential
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
FLT3	Fms-related tyrosine kinase 3
G6PD	Glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GLP	Good Laboratory Practice
GVHD	Graft-versus-host disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus

Table 16: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
HED	Human equivalent dose
HPBCD	Hydroxypropyl beta-cyclodextrin
HIV	Human immunodeficiency virus
HMA	Hypomethylating agent
HNSTD	Highest non-severely toxic dose
HR MDS	Higher-risk myelodysplastic syndromes
HPB	Hydroxypropyl beta-cyclodextrin
HSCT	Hematopoietic stem cell transplant
IC_{50}	Half maximal inhibitory concentration
ICD	Informed consent document
ICF	Informed consent form
ICH	International Council for Harmonisation
ICSH	International Council for Standardization in Hematology
IgG	Immunoglobulin G
ImiD	Immunomodulatory drug
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational Product
IPSS-R	Revised International Prognostic Scoring System score
IRB	Institutional Review Board
IRT	Integrated Response Technology
IV	Intravenous
IWG	International working group
KIT	Stem cell factor receptor
LDH	Lactate dehydrogenase
LSU	Limited stay unit
LVEF	Left ventricular ejection fraction
mCR	Marrow complete remission
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	Morphologic leukemia-free state
Mg	Magnesium

Table 16: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
MRC	Medical research council
MRD	Minimal residual disease
mRNA	Messenger RNA
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition
N	Number
NCI	National Cancer Institute
NMD	Nonsense-mediated decay
NOAEL	No observed adverse effect level
NOEL	No observable effect level
NPM1	Nucleophosmin 1
NTD	Non-tolerated dose
O_2	Oxygen
ORR	Objective response rate
OS	Overall survival
P1NP	Procollagen type 1 N-terminal propeptide
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamic or disease progression
PFS	Progression-free survival
PK	Pharmacokinetics
PO	By mouth
PPI	Proton pump inhibitor
PPP	Pregnancy prevention plan
PR	Partial remission
PT	Prothrombin time
PTH	Parathyroid hormone
PTT	Partial thromboplastin time
Q	Every
QD	Once a day
RFS	Relapse-free survival
RP2D	Recommended Phase 2 Dose
R/R	Relapsed or refractory

Table 16: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
RT-PCR	Reverse transcription-polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard operating procedure
SRC	Safety review committee
STD	Severely toxic dose
STD10	Severely toxic dose in 10%
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal half-life
t_{max}	Time to peak plasma concentration
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TEASAE	Treatment-emergent serious adverse event
TID	Three times a day
TK	Toxicokinetics
TLS	Tumor lysis syndrome
TSH	Thyroid-stimulating hormone
TTR	Time to remission/response
TTT	Time to transformation
ULN	Upper limit of normal
UPR	Unfolded protein response
US	United States
USP	US Pharmacopeia
V_{ss}	Volume of distribution
WBC	White blood cell count
WK	Week
WNL	Within normal limits

Appendix B: The World Health Organization (WHO) Classification of Acute Myeloid Leukemia (AML)

Table 17: WHO classification of AML

AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);RUNX1-RUNX1T1
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11
APL with PML-RARA
AML with t(9;11)(p21.3;q23.3);KMT2A-MLLT3
AML with t(6;9)(p23;q34.1);DEK-NUP214
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);RBM15-MKL1
Provisional entity: AML with BCR-ABL1
AML with mutated NPM1
AML with biallelic mutations of CEBPA
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis

AML = acute myelogenous leukemia; NOS = not otherwise specified.

Source: Arber, 2016.

Appendix C: Response Criteria for Acute Myeloid Leukemia

The revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia (Cheson, 2003).

Table 18: Hematologic Response According to IWG Criteria for AML

Response Criterion	Time of Assessment	Neutrophils (µL)	Platelets (µL)	Bone Marrow Blasts (%)	Other
Early Treatment assessment	7-10 days after therapy	NA	NA	< 5	
Morphologic Leukemia-free State	Varies by protocol	NA	NA	< 5	Flow cytometry EMD
Morphologic CR	Varies by protocol	≥ 1,000	≥100,000	< 5	Transfusion EMD
Cytogenetic CR (CRc)	Varies by protocol	≥ 1,000	≥100,000	< 5	Cytogenetics—normal, EMD
Molecular CR (CRm)	Varies by protocol	≥ 1,000	≥100,000	< 5	Molecular—negative, EMD
Morphologic CR with incomplete blood recovery (CRi)	Varies by protocol	Fulfill all criteria for CR except for residual neutropenia (< 1,000/µL) or thrombocytopenia (< 100,000/µL).			
Morphologic CR with partial hematologic recovery (CRh)	Per protocol	>500	>50,000	< 5	
Partial Remission	Varies by protocol	≥ 1,000	≥100,000	Decrease ≥ 50 resulting in 5 to 25	Blasts ≤ 5% if Auer rod positive
Relapse after CR	Varies by protocol	Reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow not attributable to any other cause (eg, bone marrow regeneration after consolidation therapy).			

AML = acute myelogenous leukemia; CR = complete remission; EMD = extramedullary disease; IWG = International Working Group; NA = not applicable.

Source: Cheson, 2003, Bloomfield, 2018.

Appendix D: Performance Status Criteria

Table 19: Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken, 1982.

Appendix E: The World Health Organization (WHO) Classification of the Myelodysplastic Syndromes

Table 20: WHO classifications for MDS

WHO myeloid neoplasm and acute leukemia classification	Dysplastic findings	Cytopenias[a]	PB and BM findings and cytogenetics
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	BM <5%, PB <1%, no Auer Rods Any cytogenetics, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)[b] MDS-RS and single lineage dysplasia MDS-RS and multilineage dysplasia	 1 2 or 3	 1 or 2 3	BM <5%, PB <1%, no Auer Rods Any cytogenetics, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	BM <5%, PB <1%, no Auer Rods Any cytogenetics, unless fulfills all criteria for MDS with isolated del(5q)
MDS with excess blasts (MDS-EB)			
MDS-EB-1	0-3	1-3	BM 5-9% or PB 2-4%, no Auer Rods Any cytogenetics
MDS-EB-2	0-3	1-3	BM 10-19% or PB 5-19% or Auer Rods Any cytogenetics
MDS with isolated del(5q)	1-3	1-2	BM <5%, PB <1%, no Auer Rods del(5q) alone or with 1 additional abnormality except -7 or del(7q)
MDS, unclassifiable (MDS-U)			
MDS-U with 1% blood blasts	1-3	1-3	BM <5%, PB =1%[c], no Auer Rods Any cytogenetics
MDS-U with SLD and pancytopenia	1	3	BM <5%, PB <1%, no Auer Rods Any cytogenetics
MDS-U based on defining cytogenetic abnormality	0	1-3	BM <5%, PB <1%, no Auer Rods MDS-defining abnormality[d]

[a] Cytopenias defined as : hemoglobin, <10 g/dL, platelet count, <100 x 10^9/L; and absolute neutrophil count, <1.8 x 10^9/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. Peripheral blood monocytes must be < 1 x 10^9/L.

[b] Cases with ≥ 15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

[c] One percent PB blasts must be recorded on at least 2 separate occasions.

[d] Abnormality must be demonstrated by conventional karyotyping, not by FISH or sequencing. The presence of +8, -Y, of del(20q) is not considered to be MDS-defining in the absence of diagnostic morphologic features of MDS. Sources: Arber, 2016 and Vardiman, 2009.

Appendix F: International Working Group (IWG) Response Criteria for Myelodysplasia

Table 21: Modified IWG Response Criteria for MDS

Category	Response criteria (responses must last at least 4 weeks)
Complete remission (CR)	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines[a] Persistent dysplasia will be noted[a,b] Peripheral blood[c] - Hemoglobin ≥ 11 g/dL - Platelets ≥ 100×10^9/L - Neutrophils ≥ 1.0×10^9/L[b] - Blasts 0%
Partial remission (PR)	All CR criteria if abnormal before treatment, except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Marrow CR[b] ± Hematologic Improvement (HI)	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment[b] Note: Blasts at baseline must be ≥ 5% in order for subject to be evaluable for Marrow CR[d] Peripheral blood: if HI responses, they will be noted in addition to marrow CR[b]
Stable disease (SD)	Failure to achieve at least PR, but no evidence of progression for > 8 weeks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: • Return to pretreatment bone marrow blast percentage • Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets • Reduction of Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic Response	Complete – Disappearance of the chromosomal abnormality without appearance of new ones Partial – At least 50% reduction of the chromosomal abnormality
Disease Progression (PD)	For patients with: • Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts • 5% - 10% blasts: ≥ 50% increase in blasts to > 10% blasts • 10% - 20% blasts: ≥ 50% increase in blasts to > 20% blasts Any of the following: • At least 50% decrement from maximum remission/response levels in granulocytes or platelets • Reduction in Hgb concentration by ≥ 2 g/dL • Transfusion dependence
Disease transformation	Transformation to AML (20% or more BM or PB blasts)[d]
Hematologic Improvement (HI)	
Erythroid response (HI-E) (Pretreatment < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion evaluation
Platelet response (HI-P) (Pretreatment < 100×10^9/L)	Absolute increase of ≥ 30×10^9/L for patients starting with > 20×10^9/L Increase from < 20×10^9/L to > 20×10^9/L and by at least 100%

Table 21: Modified IWG Response Criteria for MDS

Category	Response criteria (responses must last at least 4 weeks)
Neutrophil response (HI-N) (Pretreatment < 1.0×10^9/L)	At least 100% increase and an absolute increase of > 0.5×10^9/L
Progression/relapse after HI	At least one of the following: • At least 50% decrement from maximum response levels in granulocytes or platelets • Reduction in Hgb by ≥ 1.5 g/dL • Transfusion dependence

BM = bone marrow; CR = complete remission; FAB = French-American-British; Hgb = hemoglobin; HI = hematologic improvement; IWG = International Working Group; MDS = myelodysplastic syndromes; PB = peripheral blood; PD = Disease Progression; PR = partial remission; RBC = red blood cell.

[a] Dysplastic changes should consider the normal range of dysplastic changes (modification).

[b] Modification to IWG response criteria.

[c] In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such subjects can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

[d] Sponsor modification of IWG criteria.

Sources: Cheson, 2006 and Vardiman, 2009.

Table 22: RBC and Platelet Transfusion Independence

	At Screening	During Study Treatment
RBC transfusion independence	Subjects who received < 4 RBC units during the previous 56 days	Subjects who experienced a Hgb increase of 1.5 g/dL over baseline and who received no RBC transfusions during a 56-day period on treatment. Note: Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL within 3 days prior to the transfusion will count in the RBC transfusion response evaluation
RBC transfusion dependence	Subjects who received ≥ 4 RBC units during the previous 56 days	
Platelet transfusion independence	Subjects who received < 2 platelet transfusions during the previous 56 days	Subjects who received no platelet transfusions during a 56-day period on treatment
Platelet transfusion dependence	Subjects who received ≥ 2 platelet transfusions during the previous 56 days.	

RBC = red blood cell; Hgb = hemoglobin.

[a] RBC transfusion independence and RBC transfusion dependence are defined according to modified IWG criteria.

[b] Platelet transfusion independence and platelet transfusion dependence are defined by the Sponsor.

Source: Cheson, 2006.

Appendix G: Revised International Prognostic Scoring System for MDS

Table 23: IPSS-R Cytogenetic Risk Groups

Cytogenetic Prognostic Subgroups	Cytogenetic Abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: > 3 abnormalities

Source: Greenburg, 2012.

Table 24: IPSS-R Prognostic Score Values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good	-	Good	-	Inter-mediate	Poor	Very Poor
Bone Marrow Blast (%)	≤ 2	-	> 2 - < 5	-	5 - 10	> 10	-
Hemoglobin (g/dL)	≥10	-	8 - < 10	<8	-	-	-
Platelets (× 10^9/L)	≥100	50 - < 100	< 50	-	-	-	-
ANC (× 10^9/L)	≥0.8	< 0.8	-	-	-	-	-

ANC = absolute neutrophil count.
Source: Greenburg, 2012.

The total IPSS-R score is calculated as the sum of the cytogenetics, bone marrow blast percentage, hemoglobin, platelets and ANC individual scores.

Table 25: IPSS-R Prognostic Risk Categories/Scores

Risk Category	Risk Score
Very Low	≤ 1.5
Low	> 1.5 – 3
Intermediate	> 3 – 4.5
High	> 4.5 – 6
Very High	> 6

Source: Greenburg, 2012.

Table 26: IPSS-R: Prognostic Risk Category Clinical Outcomes

Prognostic variable	No. pts	Very Low	Low	Intermediate	High	Very High
Patients, %	7012	19%	38%	20%	13%	10%
Median Overall Survival (years)	-	8.8	5.3	3.0	1.6	0.8
Median time to 25% AML evolution	-	Not reached	10.8	3.2	1.4	0.73

Source: Greenberg, 2012.

Appendix H: Risk Status Based on Cytogenetics for Acute Myeloid Leukemia

Table 27: Risk Groups

Risk Status	Cytogenetics	Molecular Abnormalitiesa
Favorable-risk	Core binding factor: inv(16)[b,c,d] or t(16;16)[b,c,d] or t(8;21)[b,d] or t(15;17)[d]	Normal cytogenetics: NPM1 mutation in the absence of FLT3-ITD or isolated biallelic CEBPA mutation
Intermediate-risk	Normal cytogenetics +8 alone t(9;11) Other non-defined	Core binding factor with c-KIT mutationb
Poor-risk	Complex (≥ 3 clonal chromosomal abnormalities) Monosomal karyotype -5, 5q-, -7, 7q- 11q23 - non t(9;11) inv(3), t(3;3) t(6;9) t(9;22)[e]	Normal cytogenetics: with FLT3-ITD mutation [f] TP53 mutation

[a] The molecular abnormalities included in this table reflect those for which validated assays are available in standardized commercial laboratories. Given the rapidly evolving field, risk stratification should be modified based on continuous evaluation of research data. Other novel genetic mutations have been identified that may have prognostic significance.

[b] Emerging data indicate that the presence of KIT mutations in patients with t(8;21), and to a lesser extent inv(16), confers a higher risk of relapse. These patients are considered intermediate risk and should be considered for HSCT or clinical trials, if available. Other cytogenetic abnormalities in addition to these finding do not alter risk status.

[c] Paschka P, Du J, Schlenk RF, Gaidzik VI, Bullinger L, Corbacioglu A, et al. Secondary genetic lesions in acute myeloid leukemia with inv(16) or t(16;16): a study of the German-Austrian AML study group (AMLSG). Blood 2013; 121:170-177.

[d] Other cytogenetic abnormalities in addition to these findings do not alter better risk status

[e] For Philadelphia+ acute myeloid leukemia (AML) t(9;22), manage as myeloid blast crisis in chronic myeloid leukemia (CML), with addition of tyrosine kinase inhibitors.

[f] FLT3-ITD mutations are considered to confer a significant poorer outcome in subjects with normal karyotype, and these subjects should be considered for clinical trials where available. There is controversy as whether FLT3-TKD mutations carry equally poor prognosis

Source: NCCN, 2017a.

Appendix I: Tumor Lysis Syndrome Prophylaxis Recommendations

Table 28: Tumor Lysis Syndrome (TLS) Prophylaxis Recommendations Based on TLS Risk

Low risk disease (LRD)	Intermediate risk disease (IRD)	High risk disease (HRD)
ST*	N/A	N/A
MM	N/A	N/A
CML	N/A	N/A
Indolent NHL	N/A	N/A
HL	N/A	N/A
CLL†	N/A	N/A
AML and WBC <25 × 10^9/l and LDH <2 × ULN	AML with WBC 25–100 × 10^9/l AML and WBC <25 × 10^9/l and LDH ≥2 × ULN	AML and WBC ≥100 × 10^9/l
Adult Intermediate grade NHL and LDH <2 × ULN	Adult intermediate grade NHL and LDH ≥2 × ULN	N/A
Adult ALCL	Childhood ALCL stage III/IV	N/A
N/A	Childhood intermediate grade NHL stage III/IV with LDH <2 × ULN	N/A
N/A	ALL and WBC <100 × 10^9/l and LDH <2 × ULN	ALL and WBC ≥100 × 10^9/l and/or LDH ≥2 × ULN
N/A	BL and LDH <2 × ULN	BL stage III/IV and/or LDH ≥2 × ULN
N/A	LL stage I/II and LDH <2 × ULN	LL stage III/IV and/or LDH ≥2 × ULN
N/A	N/A	IRD with renal dysfunction and/or renal involvement IRD with uric acid, potassium and/or phosphate >ULN
Prophylaxis recommendations		
Monitoring Hydration ±Allopurinol	Monitoring Hydration Allopurinol	Monitoring Hydration Rasburicase‡

ST, solid tumours; MM, multiple myeloma; CML, chronic myeloid leukaemia; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; CLL, chronic lymphoid leukaemia; AML, acute myeloid leukaemia; WBC, white blood cell count; LDH, lactate dehydrogenase; ULN, upper limit of normal; ALCL, anaplastic large cell lymphoma; N/A, not applicable; ALL, acute lymphoblastic leukaemia; BL, Burkitt lymphoma/leukaemia; LL, lymphoblastic lymphoma.
*Rare solid tumours, such as neuroblastoma, germ cell tumours and small cell lung cancer or others with bulky or advanced stage disease, may be classified as IRD.
†CLL treated with fludarabine, rituximab and/or those with high WBC (≥50 × 10^9/l), should be classified as IRD.
‡Contraindicated in patients with a history consistent with glucose-6 phosphate dehydrogenase. In these patients, rasburicase should be substituted with allopurinol.

Source: Cairo, 2010.

Table 29: Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Uric Acid	≥ 476 µmol/l (≥ 8.0 mg/dl) or 25% increase from baseline
Potassium	≥ 6.0 mmol/l (≥ 6.0 mEq/l) or 25% increase from baseline
Phosphorous	≥ 1.45 mmol/l (≥ 4.5 mg/dl) or 25 % increase from baseline
Calcium	≤ 1.75 mmol/l (≤ 7.0 mg/dl) or 25% decrease from baseline

Source: Cairo, 2004.

Notes: Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any 2 or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a subject has or will receive adequate hydration (± alkalinization) and a hypouricemic agent(s).

The Cairo-Bishop Definition of Clinical Tumor Lysis Syndrome

The Presence of Laboratory TLS and One or More of the Following Criteria:

- Creatinine: ≥ 1.5 upper limit of normal ([ULN] age > 12 years or age-adjusted)
- Cardiac arrhythmia / sudden death
- Seizure not directly attributable to a therapeutic agent

Table 30: Cairo-Bishop Grading System for Tumor Lysis Syndrome

Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
0	-	≤ 1.5 x ULN	None	None
1	+	1.5 x ULN	Intervention not indicated	None
2	+	> 1.5 – 3.0 x ULN	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled by anti-convulsants or infrequent; focal motor seizures not interfering with ADL
3	+	> 3.0 – 6.0 x ULN	Symptomatic and incompletely controlled medically or controlled with device	Seizure in which consciousness is altered; poorly controlled seizure disorder; breakthrough generalized seizures despite medical intervention
4	+	> 6.0 x ULN	Life-Threatening	Seizures of any kind that are prolonged, repetitive, or difficult to control
5	+	Death[a]	Death	Death

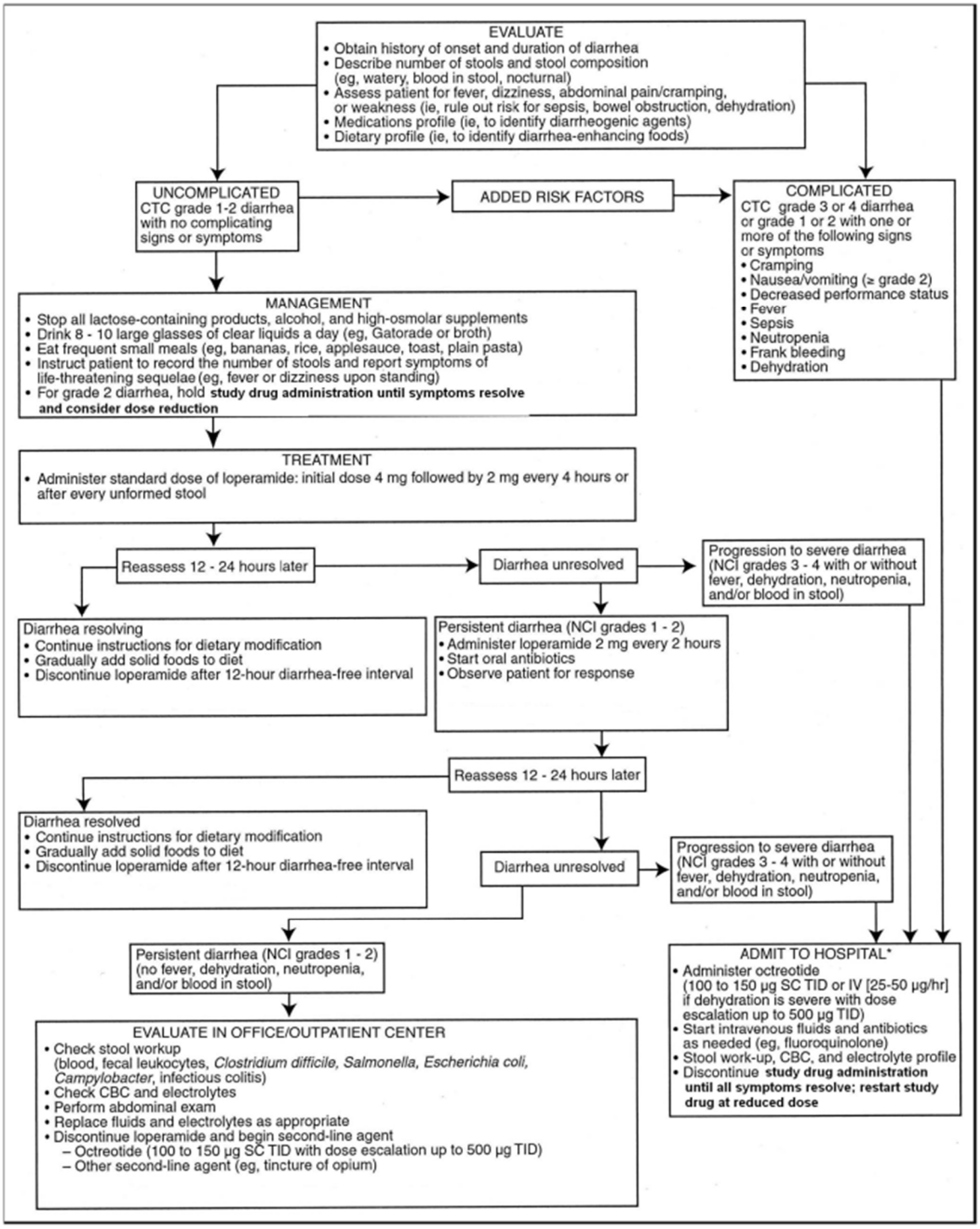
ADL = Activities of Daily Living; LTLS = Laboratory Tumor Lysis Syndrome; ULN = Upper Limit of Normal.

[a] Probably or definitely attributable to clinical TLS.

Source: Cairo, 2010.

Appendix J: Recommendations for Management of Treatment-Induced Diarrhea

The published guidelines (Benson, 2004) were modified to be consistent with the study protocol.



Source: Benson, 2004.

Appendix K: Part A Table of Events for D1-3/D8-10 Dosing Schedule

Table 31: Table of Events for Part A (D1-3/D8-10 Schedule) of Cycle 1

	Screening	Treatment Period												
		Cycle 1												
		WK1				WK2				WK3	WK4		WK5	WK6[b]
Events[a]	**D-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D8**	**D9**	**D10**	**D11**	**D15**	**D22**	**D28[c]**	**D29**	**D36**
Study Entry (Section 6.1)														
Informed consent	X													
Inclusion/ exclusion criteria	X													
Medical/ oncologic history	X													
Demographics	X													
IRT registration	X	X												
Pregnancy risk counseling and contraceptive compliance confirmation	X	As specified in Section 6.1.1 and the PPP in Appendix L.												
Prior/ concomitant medications & procedures (Section 6.2.1)	X	X	X	X	X	X	X	X	X	X	X		X	X
CC-90009 Administration (Section 7)														
Calcium, calcitriol, and vitamin D supplements and recording on diary card (Section 7.2)	X (D-3 to D-1)	X	X	X	X (D4-7)	X	X	X	X[d]			X[d]		X[d]
Provide/ review diary card	X	X												
Corticosteroid administration (dexamethasone) (refer to Section 7.2) for doses 3.6 mg and above		X	X	X		X	X	X						
IV administration of CC-90009[e]		X	X	X		X	X	X						
Monitoring as inpatient		X	X	X	X	X	X	X	X					
Safety Assessments (Section 6)														
Adverse Event Evaluation (Section 6.2.2)	X	X	X	X	X	X	X	X	X	X	X		X	X

Table 31: Table of Events for Part A (D1-3/D8-10 Schedule) of Cycle 1

	Screening	Treatment Period												
		Cycle 1												
		WK1				WK2				WK3	WK4		WK5	WK6[b]
Events[a]	**D-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D8**	**D9**	**D10**	**D11**	**D15**	**D22**	**D28[c]**	**D29**	**D36**
Height	X													
Weight (Section 6.2.3)	X	X				X				X	X			
Vital Signs (Section 6.2.3)	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X	X		X	X
Physical Examination (Section 6.2.4)	X	X				X								
ECOG PS (Appendix D)	X	X				X								
12-lead ECG (in triplicate, Section 6.2.5)	X (≥72 hrs prior to D1)	X[f]				X[f]								
LVEF (ECHO/MUGA scan; Section 6.2.6)	X													
Pregnancy testing per PPP (FCBP only; Section 6.2.7)	X[g]					X				X	X			X
Hematology laboratory tests (Section 6.2.8)	X (D-14 to -1)	X	X	X	X	X	X	X	X	X	X		X	X
G6PD (Section 6.2.8)	X													
Serum chemistry laboratory tests (Section 6.2.8)[h]	X (D-3 to -1)	X[i]	X[i]	X[i]	X	X	X	X	X	X	X		X	X
Additional serum Ca, Mg and PTH tests (Section 6.2.8)[h]		X[j]	X[j]	X[j]		X[j]	X[j]	X[j]						
Serum PTH, P1NP, β-CTx tests (Section 6.2.8)		X				X				X	X			
Serum 25-hydroxyvitamin D level (Section 6.2.8)	X	X												
Urine Ca/ creatinine ratio (random) (Section 6.2.8)		X				X				X	X			
Amylase, lipase, T-cell subsets (CD4+ and CD8+), TSH (Section 6.2.8)		X												
PT, INR, PTT (Section 6.2.8)[k]	X													

Table 31: Table of Events for Part A (D1-3/D8-10 Schedule) of Cycle 1

	Screening	Treatment Period												
		Cycle 1												
		WK1				WK2				WK3	WK4		WK5	WK6[b]
Events[a]	**D-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D8**	**D9**	**D10**	**D11**	**D15**	**D22**	**D28[c]**	**D29**	**D36**
Urinalysis (Section 6.2.8)	X (D-14 to -1)													
PK & PD Assessments														
Blood, PK (Section 6.5)		X[l]	X	X[l]	X	X[l]	X	X	X					
Urine, PK (Section 6.5) selected subjects[r]		X												
Pharmacogenomics sample (eg, buccal cells or nail clippings), (Section 6.6.1)		X												
Blood (whole), biomarker flow cytometry (Section 6.6.2)	X (D-14 to -1)	X	X	X[l]		X	X			X	X			
Blood (PBMCs), PD protein and RNA (Section 6.6.2)	X (D-14 to -1)	X	X		X	X	X							
Blood (PBMCs), PD ex vivo sensitivity assays, phenotyping & sequencing (Section 6.6.2)		X												
Blood (plasma), PD cytokines (Section 6.6.2)	X (D-14 to -1)	X	X	X	X	X	X			X				
Bone marrow aspirate and biopsy, PD biomarkers & MRD (Section 6.6.3)[m]	X (D-14 to -1)							X[n]				X[o] (±3d)		
Efficacy														
Bone marrow aspiration and biopsy, complete blood counts and examination of peripheral blood smears (Section 6.4)[o]	X (D-14 to -1)											X[o] (±3d)		X[p,q] (only on D42 ± 3d)

Abbreviations: β-CTx = beta C-terminal telopeptide; C = cycle; Ca = calcium; CD = cluster of differentiation; D = day; ECHO = echocardiogram; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FCBP = females of child bearing potential; G6PD = glucose-6-phosphate dehydrogenase; hrs = hours; INR =

international normalized ratio; IRT = integrated response technology; IV = intravenous; LVEF = left ventricular ejection fraction; Mg = magnesium; MRD = Minimal Residual Disease; MUGA = multi-gated acquisition scan; P1NP = procollagen type 1 N-terminal propeptide; PBMC = peripheral blood mononuclear cells; PD = pharmacodynamic; PK = pharmacokinetic; PPP = pregnancy prevention plan; PT = prothrombin time; PTH = parathyroid hormone; PTT = partial thromboplastin time; RNA = ribonucleic acid; TSH = thyroid-stimulating hormone; WK = week.

[a] All study visits/procedures will have a ± 2 day window and all laboratory blood samples should be drawn predose (≤ 5 hrs), unless otherwise specified in this table or Section 6.

[b] Subjects with hypoplastic bone marrow without evidence of persistent AML at the Day 28 assessment who have Grade ≥ 3 neutropenia will be followed for an additional 2 weeks for safety monitoring in Cycle 1 (total duration of 42 days; refer to Figure 1). Not all visits are shown as separate columns under Week 6, ie, Day 42 bone marrow assessment.

[c] Eligible subjects continue on to Cycle 2 (refer to Table 5). Based on the Day 28 bone marrow evaluation, subjects with a hypoplastic bone marrow without evidence of persistent leukemia who have Grade ≥ 3 neutropenia will be followed for an additional 2 weeks for safety monitoring in Cycle 1.

[d] Supplementation may be prolonged if hypocalcemia occurs (refer to Section 7.2.13.2). Subjects are to start supplements at least 3 days prior to Day 1 of Cycle 2 as per Section 7.2.

[e] Subjects will be closely monitored during administration of CC-90009 and for at least one hour after. Subjects should be adequately hydrated to prevent potential tumor lysis syndrome (TLS) (eg, 2 to 3 liters of oral or IV fluids per day) starting the day prior to CC-90009 administration and continuing through each day of CC-90009 administration. Refer to Section 7.2.12 for information on dose interruptions. The SRC may decide to evaluate alternate dosing schedules (eg, increasing from 5 to up to 10 consecutive days of CC-90009 administration) based on their review of available clinical and laboratory safety data, PK profiles, and PD findings.

[f] Multiple measurements performed on this day.

[g] Two pregnancy tests (sensitivity of at least 25 mIU/mL) must be performed prior to first dose of CC-90009: within 10 to 14 days prior and within 24 hours prior. Both tests must be negative for CC-90009 dosing to begin.

[h] A free (ionized) serum calcium test should be obtained at Screening to establish baseline values in addition to the corrected serum calcium test (corrected for albumin) used to fulfill the inclusion criteria. In the event of Grade ≥ 2 hypocalcemia or symptoms of hypocalcemia (eg, carpopedal spasm, tetany, seizures, etc), subjects must be hospitalized. Also, if Grade ≥ 2 hypocalcemia and abnormal levels of serum albumin occurs, a serum ionized calcium test must be performed. Refer to Section 7.2.13.2 for hypocalcemia management guidelines.

[i] Specific tests for TLS monitoring required predose and 12 hours (± 1 hour) postdose on Days 1, 2, and 3. Refer to Section 6.2.8.

[j] Additional serum calcium/magnesium tests required 6 and 12 hours (± 1 hour) postdose on days of CC-90009 administration. Additional PTH tests required at 6 hours (± 1 hours) post-dose on days of CC-90009 administration.

[k] Subsequent coagulation tests only performed for subjects on anticoagulant therapy and as clinically indicated.

[l] Multiple blood samples will be collected for this assay on the specified day. Refer to Sections 6.5 and 6.6.

[m] Bone marrow samples for biomarker assessment are mandatory. If bone marrow samples are scheduled to be collected on the same day for efficacy, the biomarker samples should be collected at the same time. If sufficient bone marrow aspirate specimen is not available, peripheral blood may be submitted in place of the BMA specimen for biomarker studies (eg, MRD); see laboratory manual for details.

[n] Obtained between 4 to 8 hours postdose. The samples may be obtained on Day 9 if necessary due to scheduling difficulties.

[o] Additional aspirates and biopsies will be collected as clinically indicated (eg, Cycle 1 Day 15 based on Investigator's medical assessment).

[p] Molecular and cytogenetic studies may be omitted at: Screening, if they were completed within the previous 90 days and the results are available for recording on the electronic case report forms and Day 42 (or at hematologic recovery) if a complete response is documented at Day 28.

[q] Additional bone marrow assessment performed at the time of hematologic recovery or Day 42 (± 3 days). Eligible subjects continue on to Cycle 2 (refer to Table 5).

[r] Urine PK to be performed on approximately 10 selected subjects from Part A and/or Part B. This is a 24-hour collection that starts C1D1 and ends C1D2.

Table 32: Table of Events for Part A (D1-3/D8-10 Schedule) of Cycle ≥ 2

Events[a]	Treatment Period												Follow-up Period	
	Cycles ≥2													
	WK1				WK2				WK3	WK4		EOT[b]	Safety[c]	
	D1	D2	D3	D4	D8	D9	D10	D11	D15	D22	D28	≤ 28 days	28 days (± 3 d)	Long Term
Review concomitant medications & procedures (Section 6.2.1)	X	X	X	X	X	X	X	X	X	X		X	X	
CC-90009 Administration (Section 7)														
Calcium, calcitriol and Vitamin D supplements and recording on diary card (Section 7.2)	X	X	X	X (D4-7)	X	X	X[d]				X (C2 & C3)[d]			
Provide/ review of diary card	X											X		
Corticosteroid administration (dexamethasone) (refer to Section 7.2) for doses 3.6 mg and above	X	X	X		X	X	X							
IV administration of CC-90009[e]	X	X	X		X	X	X							
Safety Assessments (Section 6)														
Adverse Event Evaluation (Section 6.2.2)	X	X	X	X	X	X	X	X	X	X		X	X	
Weight (Section 6.2.3)	X											X		
Vital Signs (Section 6.2.3)	X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X	X		X		
Physical Examination (Section 6.2.4)	X											X		
ECOG PS (Appendix D)	X											X		
12-lead ECG (Section 6.2.5)[g]	X											X		
LVEF (ECHO/MUGA; Section 6.2.6)	X (only C2 ± 7d)											X (± 7d)[h]		
Pregnancy test (FCBP only; Section 6.2.7)	X								X[i]			X[i]	X[i]	
Pregnancy risk counseling and contraceptive compliance confirmation	X	As specified in Section 6.1.1 and the PPP in Appendix L												
Hematology laboratory (Section 6.2.8)	X	X	X	X	X	X	X	X	X	X		X		
Serum chemistry laboratory tests (Section 6.2.8)[j]	X	X			X				X	X		X		
Serum Ca & Mg tests (Section 6.2.8)[j]	X[j]	X[j]	X[j]		X[j]	X[j]	X[j]							
Serum PTH, P1NP, β-CTx tests (Section 6.2.8)	X				X							X		

Table 32: Table of Events for Part A (D1-3/D8-10 Schedule) of Cycle ≥ 2

Events[a]	Treatment Period												Follow-up Period	
	Cycles ≥2													
	WK1				WK2				WK3	WK4		EOT[b]	Safety[c]	
	D1	D2	D3	D4	D8	D9	D10	D11	D15	D22	D28	≤ 28 days	28 days (± 3 d)	Long Term
Serum 25-hydroxyvitamin D level (Section 6.2.8)	X													
Urine Ca/ creatinine ratio test (random) (Section 6.2.8)	X				X							X		
Amylase, lipase, T-cell subsets (CD4+ and CD8+), TSH (Section 6.2.8)	X											X		
PT, INR, PTT (for subjects on anticoagulant therapy) (Section 6.2.8)	X											X		
Urinalysis (Section 6.2.8)	X											X		
PK/PD Assessments														
Blood, PK (Section 6.5) for Cycle 2 only	X	X	X	X	X	X	X	X						
Bone marrow aspirate and biopsy, PD biomarkers & MRD (Section 6.6.3)[k,l]											X (C2 and C4; ± 3d)	X[m]		Refer to Section 6.3.2
Efficacy														
Complete blood counts and examination of peripheral blood smears (Section 6.4)[l]											X (C2 and C4; ± 3d)	X[m]		Refer to Section 6.3.2
Bone marrow aspirate and biopsy (Section 6.4)[m]											X (C2 and C4; ± 3d)	X[m]		Refer to Section 6.3.2
Follow-up														
CC-90009-related AE/SAE follow-up	Refer to Section 6.3.1													
Anticancer therapies	Refer to Section 6.3.2													
Survival	Refer to Section 6.3.3													

Abbreviations: Adverse event = AE; β-CTx = beta C-terminal telopeptide; C = cycle; Ca = calcium; CD = cluster of differentiation; D = day; ECHO = echocardiogram; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; FCBP = females of child bearing potential; INR = international normalized ratio; IV = intravenous; LVEF = left ventricular ejection fraction; Mg = magnesium; MUGA = multi-gated acquisition scan; P1NP = procollagen type 1 N-terminal propeptide; PD = pharmacodynamic; PPP = pregnancy prevention plan; PT = prothrombin time; PTH = parathyroid hormone; PTT = partial thromboplastin time; q = every; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WK = week.

[a] All study visits/procedures will have a ± 2 day window and all laboratory blood samples should be drawn predose (≤ 5 hrs), unless otherwise specified in this table or Section 6. Cycles should start ≤ 7 days after the last day of the previous cycle.

[b] EOT Visit performed within 28 days after last dose of CC-90009 for subjects that discontinue prior to completing dosing in Cycle 4. For subjects that complete dosing in Cycle 4, this visit should be completed on Day 28 (± 2 days) of Cycle 4. For subjects who complete dosing after Cycle 4, EOT Visit should be completed within 28 days after the last day of the previous cycle.

[c] Safety Follow-up Visit is performed 28 days (± 3 days) after the last dose of CC-90009 for all subjects. May be performed by telephone contact if pregnancy testing is not required (refer to footnote "i").

[d] Supplements to be administered for at least 3 days after the last dose in each cycle. Supplementation may be prolonged if hypocalcemia occurs (refer to Section 7.2.13.2). Subjects to start supplements at least 3 days prior to Day 1 of Cycles 3 and 4 as per Section 7.2.

[e] Subjects will be closely monitored during the administration of CC-90009 and for at least 1 hour after. Subjects should be adequately hydrated to prevent potential tumor lysis syndrome (TLS) (eg, 2 to 3 liters of oral or IV fluids per day) starting the day prior to CC-90009 administration and continuing through each day of CC-90009 administration. Refer to Section 7.2.12 for information on dose interruptions. The SRC may decide to evaluate alternate dosing schedules (eg, increasing from 5 to up to 10 consecutive days of CC-90009 administration) based on their review of available clinical and laboratory safety data, PK profiles, and PD findings. Subjects should be administered CC-90009 in a Limited Stay Unit (LSU) or as in patient. Subjects experiencing Grade ≥ 2 hypocalcemia during any cycle should be administered CC-90009 in the inpatient setting for subsequent cycles (an exception can be made for subjects with grade 2 hypocalcemia lasting less than 24 hours that recovers without IV calcium [eg, calcium gluconate or calcium chloride] after discussion with the Celgene medical monitor).

[f] Multiple measurements performed on this day.

[g] Triplicate ECGs will be performed on Day 1 of each cycle (refer to Section 6.2.5) and a single ECG obtained at the EOT visit.

[h] The EOT Visit LVEF is not required if the prior LVEF was performed within 56 days.

[i] Per the PPP, a pregnancy test is required 28 days after the last dose of for all FCBP. For FCBP with irregular menstrual periods, a pregnancy test is required every 14 days (ie, Day 15 of Cycles ≥ 2 and at 14 and 28 days after the last dose of CC-90009).

[j] In the event of Grade ≥ 2 hypocalcemia or symptoms of hypocalcemia (eg, carpopedal spasm, tetany, seizures, etc), subjects must be hospitalized. Also, if Grade ≥ 2 hypocalcemia and abnormal levels of serum albumin occurs, a serum ionized calcium test must be performed. Refer to Section 7.2.13.2 for hypocalcemia management guidelines. Refer to Section 6.2.8 for required days and timing of tests. Subjects who experienced Grade ≥ 2 hypocalcemia during Cycle 1, require testing all dosing days at 6 and 12 hours postdose.

[k] Bone marrow samples for biomarker PD assessment are mandatory. When applicable (refer to time points in the table above), bone marrow samples for biomarker PD assessment will be obtained at the same time as a scheduled efficacy assessment. If sufficient bone marrow aspirate specimen is not available, peripheral blood may be submitted in place of the BMA specimen for biomarker studies (eg, MRD); see laboratory manual for details.

[l] If end of Cycle 2 (Day 28 ± 3 days) samples are obtained on Day 1 of Cycle 3, they must be obtained prior to CC-90009 administration. Additionally, bone marrow aspirates and biopsies may be obtained in both Part A and Part B, after a CR is confirmed, if relapse is suspected, or following treatment discontinuation to elucidate effects of long-term treatment or resistance mechanisms. Additional aspirates and biopsies will be collected as clinically indicated based on the Investigator's medical assessment.

[m] For subjects that complete dosing in Cycle 4, performed/obtained once on Day 28 (± 3 days). For subjects that continue (after consultation with Medical Monitor) beyond Cycle 4, efficacy and bone marrow PD assessments may be obtained to confirm a CR, if relapse is suspected, or following treatment discontinuation to elucidate effects of long-term treatment or resistance mechanisms. Additional aspirates and biopsies will be collected as clinically indicated based on the Investigator's medical assessment. Refer to Section 6.3.2 and Section 6.4.

Appendix L: CC-90009 Pregnancy Prevention Plan

Specific details regarding the CC-90009 Pregnancy Prevention Plan (PPP) will be provided via a separate, stand-alone document.

Appendix M: Part A Table of Events for D1-7 Dosing Schedule

Table 33: Table of Events for Part A (D1-7 Schedule) of Cycle 1

	Screening	Treatment Period												
		Cycle 1												
		WK1							WK2	WK3	WK4		WK5[b]	WK6[b]
Events[a]	**D-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D15**	**D22**	**D28[c]**	**D29**	**D36**
Study Entry (Section 6.1)														
Informed consent	X													
Inclusion/ exclusion criteria	X													
Medical/ oncologic history	X													
Demographics	X													
IRT registration	X	X												
Pregnancy risk counseling and contraceptive compliance confirmation	X	As specified in Section 6.1.1 and the PPP in Appendix L												
Prior/ concomitant medications & procedures (Section 6.2.1)	X	X	X	X	X	X	X	X	X	X	X		X	X
CC-90009 Administration (Section 7)														
Calcium, calcitriol, and vitamin D supplements and recording on diary card (refer to Section 7.2)	X (D-3 to D-1)	X	X	X	X	X	X	X	X[d]			X[d]		X[d]
Provide/ review diary card	X	X												
Corticosteroid administration (dexamethasone) (refer to Section 7.2) for doses 3.6 mg and above		X	X	X	X	X	X	X						
IV administration of CC-90009[e]		X	X	X	X	X	X	X						
Monitoring as inpatient		X	X	X	X	X	X	X						
Safety Assessments (Section 6)														
Adverse Event Evaluation (Section 6.2.2)	X	X	X	X	X	X	X	X	X	X	X		X	X

Table 33: Table of Events for Part A (D1-7 Schedule) of Cycle 1

	Screening	Treatment Period												
		Cycle 1												
		WK1							WK2	WK3	WK4		WK5[b]	WK6[b]
Events[a]	**D-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D15**	**D22**	**D28[c]**	**D29**	**D36**
Height	X													
Weight (Section 6.2.3)	X	X							X	X	X			
Vital Signs (Section 6.2.3)	X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X	X	X		X	X
Physical Examination (Section 6.2.4)	X	X							X					
ECOG PS (Appendix D)	X	X							X					
12-lead ECG (in triplicate, Section 6.2.5)	X (≥72 hrs prior to D1)	X[f]						X[f]	X					
LVEF (ECHO/MUGA scan; Section 6.2.6)	X													
Pregnancy testing per PPP (FCBP only; Section 6.2.7)	X[g]								X	X	X			X
Hematology laboratory tests (Section 6.2.8)	X (D-14 to -1)	X	X	X	X	X	X	X	X	X	X		X	X
G6PD (Section 6.2.8)	X													
Serum chemistry laboratory tests (Section 6.2.8)[h]	X (D-3 to -1)	X[i]	X[i]	X[i]	X	X	X	X	X	X	X		X	X
Additional serum Ca, Mg and PTH tests (Section 6.2.8)[h]		X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]						
Serum PTH, P1NP, β-CTx tests (Section 6.2.8)		X							X	X	X			
Serum 25-hydroxyvitamin D level (Section 6.2.8)	X	X												
Urine Ca/ creatinine ratio (random) (Section 6.2.8)		X							X	X	X			

Table 33: Table of Events for Part A (D1-7 Schedule) of Cycle 1

	Screening	Treatment Period												
		Cycle 1												
		WK1							WK2	WK3	WK4		WK5[b]	WK6[b]
Events[a]	**D-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D15**	**D22**	**D28[c]**	**D29**	**D36**
Amylase, lipase, T-cell subsets (CD4+ and CD8+), TSH (Section 6.2.8)		X												
PT, INR, PTT (Section 6.2.8)[k]	X													
Urinalysis (Section 6.2.8)	X (D-14 to -1)									X				
PK & PD Assessments														
Blood, PK (Section 6.5)		X[l]	X	X[l]	X			X[l]						
Urine, PK (Section 6.5) selected subjects[r]		X												
Pharmacogenomics sample (eg, buccal cells or nail clippings), (Section 6.6.1)		X												
Blood (whole), biomarker flow cytometry (Section 6.6.2)	X (D-14 to -1)	X[l]	X[l]	X[l]					X	X				
Blood (PBMCs), PD protein and RNA (Section 6.6.2)	X (D-14 to -1)	X[l]	X	X					X					
Blood (PBMCs), PD ex vivo sensitivity assays, phenotyping & sequencing (Section 6.6.2)		X												
Blood (plasma), PD cytokines (Section 6.6.2)	X (D-14 to -1)	X	X	X	X				X					
Bone marrow aspirate and biopsy, PD biomarkers & MRD (Section 6.6.3)[m]	X (D-14 to -1)							X[n]				X (± 3d)		

Table 33: Table of Events for Part A (D1-7 Schedule) of Cycle 1

	Screening	Treatment Period												
		Cycle 1												
		WK1							WK2	WK3	WK4		WK5[b]	WK6[b]
Events[a]	D-28 to -1	D1	D2	D3	D4	D5	D6	D7	D8	D15	D22	D28[c]	D29	D36
Efficacy														
Bone marrow aspiration and biopsy, complete blood counts and examination of peripheral blood smears (Section 6.4)[o]	X (D-14 to -1)[p]											X (± 3d)		X (only on D42 ± 3d)[q]

Abbreviations: β-CTx = beta C-terminal telopeptide; C = cycle; Ca = calcium; CD = cluster of differentiation; D = day; ECHO = echocardiogram; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FCBP = females of child bearing potential; G6PD = glucose-6-phosphate dehydrogenase; hrs = hours; INR = international normalized ratio; IRT = integrated response technology; IV = intravenous; LVEF = left ventricular ejection fraction; Mg = magnesium; MRD = Minimal Residual Disease; MUGA = multi-gated acquisition scan; P1NP = procollagen type 1 N-terminal propeptide; PBMC = peripheral blood mononuclear cells; PD = pharmacodynamic; PK = pharmacokinetic; PPP = pregnancy prevention plan; PT = prothrombin time; PTH = parathyroid hormone; PTT = partial thromboplastin time; RNA = ribonucleic acid; TSH = thyroid-stimulating hormone; WK = week.

[a] All study visits/procedures will have a ± 2 day window and all laboratory blood samples should be drawn predose (≤ 5 hrs), unless otherwise specified in this table or Section 6.

[b] Subjects with hypoplastic bone marrow without evidence of persistent AML at the Day 28 assessment who have Grade ≥ 3 neutropenia will be followed for an additional 2 weeks for safety monitoring in Cycle 1 (total duration of 42 days; refer to Figure 1). Not all visits are shown as separate columns under Week 6, ie, Day 42 bone marrow assessment.

[c] Eligible subjects continue on to Cycle 2 (refer to Table 5). Based on the Day 28 bone marrow evaluation, subjects with a hypoplastic bone marrow without evidence of persistent leukemia who have Grade ≥ 3 neutropenia will be followed for an additional 2 weeks for safety monitoring in Cycle 1.

[d] Supplementation may be prolonged if hypocalcemia occurs (refer to Section 7.2.13.2). Subjects are to start supplements at least 3 days prior to Day 1 of Cycle 2 as per Section 7.2.

[e] Subjects will be closely monitored during administration of CC-90009 and for at least one hour after. Subjects should be adequately hydrated to prevent potential tumor lysis syndrome (TLS) (eg, 2 to 3 liters of oral or IV fluids per day) starting the day prior to CC-90009 administration and continuing through each day of CC-90009 administration. Refer to Section 7.2.12 for information on dose interruptions. The SRC may decide to evaluate alternate dosing schedules (eg, increasing from 5 to up to 10 consecutive days of CC-90009 administration) based on their review of available clinical and laboratory safety data, PK profiles, and PD findings.

[f] Multiple measurements performed on this day.

[g] Two pregnancy tests (sensitivity of at least 25 mIU/mL) must be performed prior to first dose of CC-90009: within 10 to 14 days prior and within 24 hours prior. Both tests must be negative for CC-90009 dosing to begin.

[h] A free (ionized) serum calcium test should be obtained at Screening to establish baseline values in addition to the corrected serum calcium test (corrected for albumin) used to fulfill the inclusion criteria. In the event of Grade ≥ 2 hypocalcemia or symptoms of hypocalcemia (eg, carpopedal spasm, tetany, seizures, etc), subjects must be hospitalized. Also, if Grade ≥ 2 hypocalcemia and abnormal levels of serum albumin occurs, a serum ionized calcium test must be performed. Refer to Section 7.2.13.2 for hypocalcemia management guidelines.

[i] Specific tests for TLS monitoring required predose and 12 hours (± 1 hour) postdose on Days 1, 2, and 3. Refer to Section 6.2.8.

[j] Additional serum calcium/magnesium tests required 6 and 12 hours (± 1 hour) postdose on days of CC-90009 administration. Additional PTH tests required at 6 hours (± 1 hours) post-dose on days of CC-90009 administration.

[k] Subsequent coagulation tests only performed for subjects on anticoagulant therapy and as clinically indicated.

[l] Multiple blood samples will be collected for this assay on the specified day. Refer to Sections 6.5 and 6.6.

[m] Bone marrow samples for biomarker assessment are mandatory. If bone marrow samples are scheduled to be collected on the same day for efficacy, the biomarker samples should be collected at the same time. If sufficient bone marrow aspirate specimen is not available, peripheral blood may be submitted in place of the BMA specimen for biomarker studies (eg, MRD); see laboratory manual for details.

[n] Obtained between 4 to 8 hours postdose. The samples may be obtained on Day 6 or Day 8 if necessary due to scheduling difficulties. If the dosing interval (schedule) is extended, then samples will be obtained on the last day ±1 day of dosing (eg, if extended to 10 day, obtain on Day 9-11).

[o] Additional aspirates and biopsies will be collected as clinically indicated (eg, Cycle 1 Day 15 based on Investigator's medical assessment).

[p] Molecular and cytogenetic studies may be omitted at: Screening, if they were completed within the previous 90 days and the results are available for recording on the electronic case report forms and Day 42 (or at hematologic recovery), if a complete response is documented at Day 28.

[q] Additional bone marrow assessment performed at the time of hematologic recovery or Day 42 (± 3 days). Eligible subjects continue on to Cycle 2 (refer to Table 5).

[r] Urine PK to be performed on approximately 10 selected subjects from Part A and/or Part B. This is a 24-hour collection that starts on C1D1 and ends on C1D2.

Table 34: Table of Events for Part A (D1-7 Schedule) of Cycles ≥ 2

	Treatment Period												Follow-up Period	
	Cycles ≥ 2													
	WK1							WK2	WK3	WK4		EOT[b]	Safety[c]	
Events[a]	D1	D2	D3	D4	D5	D6	D7	D8	D15	D22	D28	≤ 28 days	28 days (± 3 days)	Long Term
Review concomitant medications & procedures (Section 6.2.1)	X	X	X	X	X	X	X	X	X	X		X	X	
CC-90009 Administration (Section 7)														
Calcium, calcitriol and Vitamin D supplements and recording on diary card (Section 7.2)	X	X	X	X	X	X	X	X[d]			X (C2 and C3)[d]			
Provide/ review of diary card	X											X		
Corticosteroid administration (dexamethasone) (refer to Section 7.2) for doses 3.6 mg and above	X	X	X	X	X	X	X							
IV administration of CC-90009[e]	X	X	X	X	X	X	X							
Safety Assessments (Section 6)														
Adverse Event Evaluation (Section 6.2.2)	X	X	X	X	X	X	X	X	X	X		X	X	
Weight (Section 6.2.3)	X											X		
Vital Signs (Section 6.2.3)	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X	X	X		X		
Physical Examination (Section 6.2.4)	X											X		
ECOG PS (Appendix D)	X											X		
12-lead ECG (Section 6.2.5)[g]	X											X		
LVEF (ECHO/MUGA; Section 6.2.6)	X (only C2 ± 7d)											X (± 7d)h		
Pregnancy test (FCBP only; Section 6.2.7)	X								X[i]			Xi	Xi	

Table 34: Table of Events for Part A (D1-7 Schedule) of Cycles ≥ 2

Events[a]	Treatment Period												Follow-up Period	
	Cycles ≥ 2													
	WK1							WK2	WK3	WK4		EOT[b]	Safety[c]	
	D1	D2	D3	D4	D5	D6	D7	D8	D15	D22	D28	≤ 28 days	28 days (± 3 days)	Long Term
Pregnancy risk counseling and contraceptive compliance confirmation	X	As specified in Section 6.1.1 and the PPP in Appendix L												
Hematology laboratory (Section 6.2.8)	X	X	X	X	X	X	X	X	X	X		X		
Serum chemistry laboratory tests (Section 6.2.8)[j]	X	X						X	X	X		X		
Serum Ca & Mg tests (Section 6.2.8)[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]							
Serum PTH, P1NP, β-CTx tests (Section 6.2.8)	X						X					X		
Serum 25-hydroxyvitamin D level (Section 6.2.8)	X													
Urine Ca/ creatinine ratio test (random) (Section 6.2.8)	X						X					X		
Amylase, lipase, T-cell subsets (CD4+ and CD8+), TSH (Section 6.2.8)	X											X		
PT, INR, PTT (for subjects on anticoagulant therapy) (Section 6.2.8)	X											X		
Urinalysis (Section 6.2.8)	X											X		
PK & PD Assessments														
Blood, PK (Section 6.5)[o]	X	X	X	X			X[o]							
Blood (whole), biomarker flow cytometry, (Section 6.6.2) first cycle of intra-subject dose escalation only[k]	X[k]	X[k]	X[k]					X[k]	X[k]					
Blood (PBMCs), PD protein and RNA (Section 6.6.2) first cycle of intra-subject dose escalation only[k]	X[k]	X[k]	X[k]					X[k]						

Table 34: Table of Events for Part A (D1-7 Schedule) of Cycles ≥ 2

	Treatment Period												Follow-up Period	
	Cycles ≥ 2													
	WK1							WK2	WK3	WK4		EOT[b]	Safety[c]	
Events[a]	D1	D2	D3	D4	D5	D6	D7	D8	D15	D22	D28	≤ 28 days	28 days (± 3 days)	Long Term
Blood (plasma), PD cytokines (Section 6.6.2) first cycle of intra-subject dose escalation only[k]	X	X	X	X				X						
Bone marrow aspirate and biopsy, PD biomarkers & MRD (Section 6.6.3)[l, m]											X (C2 and C4; ± 3d)	X[n]		Refer to Section 6.3.2
Efficacy														
Complete blood counts and examination of peripheral blood smears (Section 6.4)[m]											X (C2 and C4; ± 3d)	X[n]		Refer to Section 6.3.2
Bone marrow aspirate and biopsy (Section 6.4)[m]											X (C2 and C4; ± 3d)	X[n]		Refer to Section 6.3.2
Follow-up														
CC-90009-related AE/SAE follow-up	Refer to Section 6.3.1													
Anticancer therapies	Refer to Section 6.3.2													
Survival	Refer to Section 6.3.3													

Abbreviations: Adverse event = AE; β-CTx = beta C-terminal telopeptide; C = cycle; Ca = calcium; CD = cluster of differentiation; D = day; ECHO = echocardiogram; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; FCBP = females of child bearing potential; INR = international normalized ratio; IV = intravenous; LVEF = left ventricular ejection fraction; Mg = magnesium; MUGA = multi-gated acquisition scan; P1NP = procollagen type 1 N-terminal propeptide; PD = pharmacodynamics; PPP = pregnancy prevention plan; PT = prothrombin time; PTH = parathyroid hormone; PTT = partial thromboplastin time; q = every; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WK = week.

[a] All study visits/procedures will have a ± 2 day window and all laboratory blood samples should be drawn predose (≤ 5 hrs), unless otherwise specified in this table or Section 6. Cycles should start ≤ 7 days after the last day of the previous cycle.

[b] EOT Visit performed within 28 days after last dose of CC-90009 for subjects that discontinue prior to completing dosing in Cycle 4. For subjects that complete dosing in Cycle 4, this visit should be completed on Day 28 (± 2 days) of Cycle 4. For subjects who complete dosing after Cycle 4, EOT Visit should be completed within 28 days after the last day of the previous cycle.

[c] Safety Follow-up Visit is performed 28 days (± 3 days) after the last dose of CC-90009 for all subjects. May be performed by telephone contact if pregnancy testing is not required (refer to footnote "i").

[d] Supplements to be administered for at least 3 days after the last dose in each cycle. Supplementation may be prolonged if hypocalcemia occurs (refer to Section 7.2.13.2). Subjects to start supplements at least 3 days prior to Day 1 of Cycles 3 and 4 as per Section 7.2.

[e] Subjects will be closely monitored during the administration of CC-90009 and for at least 1 hour after. Subjects should be adequately hydrated to prevent potential tumor lysis syndrome (TLS) (eg, 2 to 3 liters of oral or IV fluids per day) starting the day prior to CC-90009 administration and continuing through each day of CC-90009 administration. Refer to Section 7.2.12 for information on dose interruptions. The SRC may decide to evaluate alternate dosing schedules (eg, increasing from 5 to up to 10 consecutive days of CC-90009 administration) based on their review of available clinical and laboratory safety data, PK profiles, and PD findings. Subjects should be administered Cycle ≥ 2 of CC-90009 in a Limited Stay Unit (LSU) or as in patient. Subjects experiencing Grade ≥ 2 hypocalcemia during any cycle should be administered CC-90009 in the inpatient setting for subsequent cycles (an exception can be made for subjects with grade 2 hypocalcemia lasting less than 24 hours that recovers without IV calcium [eg, calcium gluconate or calcium chloride] after discussion with the Celgene medical monitor).

[f] Multiple measurements performed on this day.

[g] Triplicate ECGs will be performed on Day 1 of each cycle (refer to Section 6.2.5) and a single ECG obtained at the EOT visit.

[h] The EOT Visit LVEF is not required if the prior LVEF was performed within 56 days.

[I] Per the PPP, a pregnancy test is required 28 days after the last dose of for all FCBP. For FCBP with irregular menstrual periods, a pregnancy test is required every 14 days (ie, Day 15 of Cycles ≥ 2 and at 14 and 28 days after the last dose of CC-90009).

[j] In the event of Grade ≥ 2 hypocalcemia or symptoms of hypocalcemia (eg, carpopedal spasm, tetany, seizures, etc), subjects must be hospitalized. Also, if Grade ≥ 2 hypocalcemia and abnormal levels of serum albumin occurs, a serum ionized calcium test must be performed. Refer to Section 7.2.13.2 for hypocalcemia management guidelines. Refer to Section 6.2.8 for required days and timing of tests. Subjects who experienced Grade ≥ 2 hypocalcemia during Cycle 1, require testing Days 1-7 at 6 and 12 hours postdose. All other subjects require testing prior to dosing. If intra-subject dose escalation occurs, subjects should be treated as in Cycle 1.

[k] If intra-subject dose escalation occurs, blood samples for PD assays will be collected during the first cycle only at the increased dose; see laboratory manual for details. Multiple blood samples will be collected for this assay on the specified Days 1, 2, 3. Refer to Section 6.6.

[l] Bone marrow samples for biomarker PD assessment are mandatory. When applicable (refer to time points in the table above), bone marrow samples for biomarker PD assessment will be obtained at the same time as a scheduled efficacy assessment. If sufficient bone marrow aspirate specimen is not available, peripheral blood may be submitted in place of the BMA specimen for biomarker studies (eg, MRD); see laboratory manual for details.

[m] If end of Cycle 2 (Day 28 ± 3 days) samples are obtained on Day 1 of Cycle 3, they must be obtained prior to CC-90009 administration. Additionally, bone marrow aspirates and biopsies may be obtained in both Part A and Part B, after a CR is confirmed, if relapse is suspected, or following treatment discontinuation to elucidate effects of long-term treatment or resistance mechanisms. Additional aspirates and biopsies will be collected as clinically indicated based on the Investigator's medical assessment.

[n] For subjects that complete dosing in Cycle 4, performed/obtained once on Day 28 (± 3 days). For subjects that continue (after consultation with Medical Monitor) beyond Cycle 4, efficacy and bone marrow PD assessments may be obtained to confirm a CR, if relapse is suspected, or following treatment discontinuation to elucidate effects of long-term treatment or resistance mechanisms. Additional aspirates and biopsies will be collected as clinically indicated based on the Investigator's medical assessment. Refer to Section 6.3.2 and Section 6.4.

[o] Blood samples for PK are to be collected in Cycle 2 only; on Day 7 there is a pre-dose and 24 hour postdose sample Section 6.5.1.

Appendix N: Part B Table of Events for D1-7 Dosing Schedule

Table 35: Table of Events for Part B (D1-7 Schedule) of Cycle 1

	Screening	Treatment Period										
		Cycle 1										
		WK1							WK2	WK3	WK4	
Events[a]	**D-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D15**	**D22**	**D28[c]**
Study Entry (Section 6.1)												
Informed consent	X											
Inclusion/ exclusion criteria	X											
Medical[f]/ oncologic history	X											
AML or MDS Disease Assessment and Cohort Assignment[b]	X											
Demographics	X											
IRT registration	X	X										
Pregnancy risk counseling and contraceptive compliance confirmation	X	As specified in Section 6.1.1 and the PPP in Appendix L										
Prior/ concomitant medications & procedures (Section 6.2.1)	X	X	X	X	X	X	X	X	X	X	X	
CC-90009 Administration (Section 7)												
Calcium, calcitriol, and vitamin D supplements and recording on diary card (refer to Section 7.2)	X (D-3 to D-1)	X	X	X	X	X	X	X	X[d]			
Provide/review diary card	X	X										
Corticosteroid administration (dexamethasone) (refer to Section 7.2) for doses 3.6 mg and above		X	X	X	X	X	X	X				
IV administration of CC-90009		X	X	X	X	X	X	X				

Table 35: Table of Events for Part B (D1-7 Schedule) of Cycle 1

	Screening	Treatment Period										
		Cycle 1										
		WK1							WK2	WK3	WK4	
Events[a]	**D-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D15**	**D22**	**D28**[c]
Monitoring as an inpatient		X	X	X	X	X	X	X				
Safety Assessments (Section 6)												
Adverse Event Evaluation (Section 6.2.2)	X	X	X	X	X	X	X	X	X	X	X	
Height	X											
Weight (Section 6.2.3)	X	X							X	X	X	
Vital Signs (Section 6.2.3)	X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X	X	X	
Physical Examination (Section 6.2.4)	X	X							X			
ECOG PS (Appendix D)	X	X							X			
SARS-CoV-2 Viral Testing[r]	X (within 7 days of D1)											
12-lead ECG (in triplicate, Section 6.2.5)	X (≥72 hrs prior to D1)	X[f]						X[f]	X			
Adverse Event Evaluation (Section 6.2.2)	X	X	X	X	X	X	X	X	X	X	X	
Height	X											
Weight (Section 6.2.3)	X	X							X	X	X	
Vital Signs (Section 6.2.3)	X	Xf	Xf	Xf	Xf	Xf	Xf	Xf	X	X	X	
Physical Examination (Section 6.2.4)	X	X							X			
Safety Assessments (Section 6)												
ECOG PS (Appendix D)	X	X							X			

Table 35: Table of Events for Part B (D1-7 Schedule) of Cycle 1

	Screening	Treatment Period										
		Cycle 1										
		WK1							WK2	WK3	WK4	
Events[a]	**D-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D15**	**D22**	**D28**[c]
12-lead ECG (in triplicate, Section 6.2.5)	X (≥72 hrs prior to D1)	X[f]						X[f]	X			
LVEF (ECHO/MUGA scan; Section 6.2.6)	X											
Pregnancy testing per PPP (FCBP only; Section 6.2.7)	X[g]								X	X	X	
Hematology laboratory tests (Section 6.2.8)	X (D-14 to -1)	X	X	X	X	X	X	X	X	X	X	
G6PD (Section 6.2.8)	X											
Serum chemistry laboratory tests (Section 6.2.8)[h]	X (D-3 to -1)	X[i]	X[i]	X[i]	X	X	X	X	X	X	X	
Additional serum Ca, Mg and PTH tests (Section 6.2.8)[h]		X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]				
Serum 25-hydroxyvitamin D level (Section 6.2.8)	X	X										
Serum PTH, P1NP, β-CTx tests Urine Ca/ creatinine ratio (random) (Section 6.2.8)		X							X	X	X	
Amylase, lipase, T-cell subsets (CD4+ and CD8+), TSH (Section 6.2.8)		X										
PT, INR, PTT (Section 6.2.8)[k]	X											
Urinalysis (Section 6.2.8)	X (D-14 to -1)									X		
PK & PD Assessments												
Blood, PK (Section 6.5)		X[l]	X									

Table 35: Table of Events for Part B (D1-7 Schedule) of Cycle 1

	Screening	Treatment Period										
		Cycle 1										
		WK1							WK2	WK3	WK4	
Events[a]	**D-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D15**	**D22**	**D28**[c]
Pharmacogenomics sample (eg, buccal cells or nail clippings), (Section 6.6.1)		X										
SARS-CoV-2 serology[s] (Section 6.6.4)		X										
Blood (whole), biomarker flow cytometry (Section 6.6.2)	X (D-14 to -1)	X[l]		X[l]					X			X
Blood (whole), PD biomarker (Section 6.6.2)	X (D-14 to -1)							X[n]				X (± 3d)
Blood (PBMCs), PD protein and RNA (Section 6.6.2)	X (D-14 to -1)	X		X					X			
Blood (PBMCs), PD ex vivo sensitivity assays, phenotyping & sequencing (Section 6.6.2)		X										
Blood (plasma), PD cytokines (Section 6.6.2	X (D-14 to -1)	X	X	X	X				X			
Bone marrow aspirate and biopsy, PD biomarkers & MRD (Section 6.6.3)[m]	X (D-14 to -1)							X[n]				X (± 3d)
Efficacy												
Bone marrow aspiration and biopsy, complete blood counts and examination of peripheral blood smears (Section 6.4)[o]	X (D-14 to -1)[p]											X (± 3d)

Abbreviations: β-CTx = beta C-terminal telopeptide; C = cycle; Ca = calcium; CD = cluster of differentiation; D = day; ECHO = echocardiogram; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FCBP = females of child bearing potential; G6PD = glucose-6-phosphate dehydrogenase; hrs = hours; INR = international normalized ratio; IRT = integrated response technology; IV = intravenous; LVEF = left ventricular ejection fraction; Mg = magnesium; MRD = Minimal Residual Disease; MUGA = multi-gated acquisition scan; P1NP = procollagen type 1 N-terminal propeptide; PBMC = peripheral blood mononuclear cells; PD =pharmacodynamics; PK =

pharmacokinetic; PPP = pregnancy prevention plan; PT = prothrombin time; PTH = parathyroid hormone; PTT = partial thromboplastin time; RNA = ribonucleic acid; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; TSH = thyroid-stimulating hormone; WK = week.

[a] All study visits/procedures will have a ± 2 day window and all laboratory blood samples should be drawn predose (≤ 5 hrs), unless otherwise specified in this table or Section 6.

[b] See Section 6.1 for details regarding collecting BMA/BMB, PBS, and cytogenetics at screening for assessing AML/MDS diagnosis, for potential retrospective confirmation of mutational status, and collecting BMA and PB at screening for pharmacodynamics and correlative studies. A bone marrow biopsy can be collected in conjunction with an aspirate if it is standard institutional practice. A bone marrow biopsy must be collected if adequate aspirate sample is not attainable.

[c] Eligible subjects continue on to Cycle 2 (refer to Table 36).

[d] Supplementation may be prolonged if hypocalcemia occurs (refer to Section 7.2.13.2). Subjects are to start supplements at least 3 days prior to Day 1 of Cycle 2 as per Section 7.2.

[e] Subjects will be closely monitored during administration of CC-90009 and for at least one hour after. Subjects should be adequately hydrated to prevent potential tumor lysis syndrome (TLS) (eg, 2 to 3 liters of oral or IV fluids per day) starting the day prior to CC-90009 administration and continuing through each day of CC-90009 administration. Refer to Section 7.2.12 for information on dose interruptions. The SRC may decide to evaluate alternate dosing schedules (eg, increasing from 5 to up to 10 consecutive days of CC-90009 administration) based on their review of available clinical and laboratory safety data, PK profiles, and PD findings.

[f] Multiple measurements performed on this day.

[g] Two pregnancy tests (sensitivity of at least 25 mIU/mL) must be performed prior to first dose of CC-90009: within 10 to 14 days prior and within 24 hours prior. Both tests must be negative for CC-90009 dosing to begin.

[h] A free (ionized) serum calcium test should be obtained at Screening to establish baseline values in addition to the corrected serum calcium test (corrected for albumin) used to fulfill the inclusion criteria. In the event of Grade ≥ 2 hypocalcemia or symptoms of hypocalcemia (eg, carpopedal spasm, tetany, seizures, etc), subjects must be hospitalized. Also, if Grade ≥ 2 hypocalcemia and abnormal levels of serum albumin occurs, a serum ionized calcium test must be performed. Refer to Section 7.2.13.2 for hypocalcemia management guidelines.

[i] Specific tests for TLS monitoring required predose and 12 hours (± 1 hour) postdose on Days 1, 2, and 3. Refer to Section 6.2.8.

[j] Additional serum calcium/magnesium tests required 6 and 12 hours (± 1 hour) postdose on days of CC-90009 administration. Additional PTH tests required at 6 hours (± 1 hours) post-dose on days of CC-90009 administration.

[k] Subsequent coagulation tests only performed for subjects on anticoagulant therapy and as clinically indicated.

[l] Multiple blood samples will be collected for this assay on the specified day. Refer to Sections 6.5 and 6.6.

[m] Bone marrow samples for biomarker assessment are mandatory. If bone marrow samples are scheduled to be collected on the same day for efficacy, the biomarker samples should be collected at the same time. If sufficient bone marrow aspirate specimen is not available, peripheral blood may be submitted in place of the BMA specimen for biomarker studies (eg, MRD); see laboratory manual for details.

[n] Obtained between 4 to 8 hours postdose. The samples may be obtained on Day 6 or on Day 8 if necessary due to scheduling difficulties. If the dosing interval (schedule) is extended, then samples will be obtained on the last day ±1 day of dosing (eg, if extended to 10 day, obtain on Day 9-11).

[o] Additional aspirates and biopsies will be collected as clinically indicated (eg, Cycle 1 Day 15 based on Investigator's medical assessment).

[p] Molecular and cytogenetic studies may be omitted at: Screening, if they were completed within the previous 90 days and the results are available for recording on the electronic case report forms; see Section 6.1 for details on sending samples to the central laboratory.

[q] Urine PK to be performed on approximately 10 selected subjects from Part A and/or Part B. This is a 24-hour collection that starts C1D1 and ends C1D2.

[r] RT-PCR testing for SARS-CoV-2 is mandatory within 7 days prior to first dose of CC-90009 (C1D1). The RT-PCR test should be based on institutional or local guidelines. Please see Section 6.1 in the event of a positive result.

[s] Serum will be collected at predose on Cycle 1 Day 1 (or at screening), approximately every 6 months during study treatment and at EOT to be used for possible measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG). Results will not be used to determine eligibility. Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection.

[t] Medical history will also include COVID-19 vaccines, toxicities of prior treatments, and known allergies.

Table 36: Table of Events for Part B (D1-7 Schedule) of Cycles ≥ 2

Events[a]	Treatment Period												Follow-up Period	
	Cycles ≥ 2													
	WK1							WK2	WK3	WK4		EOT[b]	Safety[c]	
	D1	D2	D3	D4	D5	D6	D7	D8	D15	D22	D28	≤ 28 days	28 days (± 3 days)	Long Term
Review concomitant medications & procedures (Section 6.2.1)	X	X	X	X	X	X	X	X	X	X	X	X	X	
CC-90009 Administration (Section 7)														
Calcium, calcitriol and Vitamin D supplements and recording on diary card (Section 7.2)	X	X	X	X	X	X	X	X[d]			X (C2 and C3)[d]			
Provide/ review of diary card	X											X		
Corticosteroid administration (dexamethasone) (refer to Section 7.2) for doses 3.6 mg and above	X	X	X	X	X	X	X							
IV administration of CC-90009[e]	X	X	X	X	X	X	X							
Safety Assessments (Section 6)														
Adverse Event Evaluation (Section 6.2.2)	X	X	X	X	X	X	X	X	X	X		X	X	
Weight (Section 6.2.3)	X											X		
Vital Signs (Section 6.2.3)	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X	X	X		X		
Physical Examination (Section 6.2.4)	X											X		
ECOG PS (Appendix D)	X											X		
12-lead ECG (Section 6.2.5)[g]	X											X		
LVEF (ECHO/MUGA; Section 6.2.6)	X (only C2 ± 7d)											X (± 7d)[h]		

Table 36: Table of Events for Part B (D1-7 Schedule) of Cycles ≥ 2

Events[a]	Treatment Period												Follow-up Period	
	Cycles ≥ 2													
	WK1							WK2	WK3	WK4		EOT[b]	Safety[c]	
	D1	D2	D3	D4	D5	D6	D7	D8	D15	D22	D28	≤ 28 days	28 days (± 3 days)	Long Term
Pregnancy risk counseling and contraceptive compliance confirmation	X	As specified in Section 6.1.1 and the PPP in Appendix L												
Pregnancy test (FCBP only; Section 6.2.7)	X								X[i]			X[i]	X[i]	
Hematology laboratory (Section 6.2.8)	X	X	X	X	X	X	X	X	X	X		X		
Serum chemistry laboratory tests (Section 6.2.8)[j]	X	X						X	X	X		X		
Serum Ca & Mg tests (Section 6.2.8)[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]							
Serum PTH, P1NP, β-CTx tests (Section 6.2.8)	X						X					X		
Serum 25-hydroxyvitamin D level (Section 6.2.8)	X													
Urine Ca/ creatinine ratio test (random) (Section 6.2.8)	X						X					X		
Amylase, lipase, T-cell subsets (CD4+ and CD8+), TSH (Section 6.2.8)	X											X		
PT, INR, PTT (for subjects on anticoagulant therapy) (Section 6.2.8)	X											X		
Urinalysis (Section 6.2.8)	X											X		
PK & PD Assessments														
Blood, PK (Section 6.5)[o]						X[o]	X[o]							

Table 36: Table of Events for Part B (D1-7 Schedule) of Cycles ≥ 2

Events[a]	Treatment Period											Follow-up Period	
	Cycles ≥ 2												
	WK1							WK2	WK3	WK4		EOT[b]	Safety[c]	
	D1	D2	D3	D4	D5	D6	D7	D8	D15	D22	D28	≤ 28 days	28 days (± 3 days)	Long Term
Blood (whole), PD biomarker (Section 6.6.2)											X (C2 and C4; ± 3d)	X[n]		Refer to Section 6.3.2
Bone marrow aspirate and biopsy, PD biomarkers & MRD (Section 6.6.3)[l, m]											X (C2 and C4; ± 3d)	X[n]		Refer to Section 6.3.2
SARS-CoV-2 Serology[p] (Section 6.6.4)	Serum collected every 6 months during study treatment (eg, C6D1, C12D1, etc)											X		
Efficacy														
Complete blood counts and examination of peripheral blood smears (Section 6.4)[m]											X (C2 and C4; ± 3d)	X[n]		Refer to Section 6.3.2
Bone marrow aspirate and/or biopsy (Section 6.4)[m]											X (C2 and C4; ± 3d)	X[n]		Refer to Section 6.3.2
Follow-up														
CC-90009-related AE/SAE follow-up	Refer to Section 6.3.1													
Anticancer therapies	Refer to Section 6.3.2													
Survival	Refer to Section 6.3.3													
Transformation to AML for MDS	After signing ICF and until death, lost to follow-up, withdrawal of consent for further data collection, or end of trial.													

Abbreviations: Adverse event = AE; AML = acute myeloid leukemia; β-CTx = beta C-terminal telopeptide; C = cycle; Ca = calcium; CD = cluster of differentiation; D = day; ECHO = echocardiogram; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; FCBP = females of child bearing potential; INR = international normalized ratio; IV = intravenous; LVEF = left ventricular ejection fraction; MDS = myelodysplastic syndromes; Mg = magnesium; MUGA = multi-gated acquisition scan; P1NP = procollagen type 1 N-terminal propeptide; PD = pharmacodynamic; PK = pharmacokinetic; PPP = pregnancy prevention plan; PT = prothrombin time; PTH = parathyroid hormone; PTT = partial thromboplastin time; q = every; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WK = week.

[a] All study visits/procedures will have a ± 2 day window and all laboratory blood samples should be drawn predose (≤ 5 hrs), unless otherwise specified in this table or Section 6. Cycles should start ≤ 7 days after the last day of the previous cycle.

[b] EOT Visit performed within 28 days after last dose of CC-90009 for subjects that discontinue prior to completing dosing in Cycle 4. For subjects that complete dosing in Cycle 4, this visit should be completed on Day 28 (± 2 days) of Cycle 4. For subjects who complete dosing after Cycle 4, EOT Visit should be completed within 28 days after the last day of the previous cycle.

[c] Safety Follow-up Visit is performed 28 days (± 3 days) after the last dose of CC-90009 for all subjects. May be performed by telephone contact if pregnancy testing is not required (refer to footnote "i").

[d] Supplements to be administered for at least 3 days after the last dose in each cycle. Supplementation may be prolonged if hypocalcemia occurs (refer to Section 7.2.13.2). Subjects to start supplements at least 3 days prior to Day 1 of Cycles 3 and 4 as per Section 7.2.

[e] Subjects will be closely monitored during the administration of CC-90009 and for at least 1 hour after. Subjects should be adequately hydrated to prevent potential tumor lysis syndrome (TLS) (eg, 2 to 3 liters of oral or IV fluids per day) starting the day prior to CC-90009 administration and continuing through each day of CC-90009 administration. Refer to Section 7.2.12 for information on dose interruptions. The SRC may decide to evaluate alternate dosing schedules (eg, increasing from 5 to up to 10 consecutive days of CC-90009 administration) based on their review of available clinical and laboratory safety data, PK profiles, and PD findings. Subjects should be administered Cycle ≥ 2 of CC-90009 in a Limited Stay Unit (LSU) or as in patient. Subjects experiencing Grade ≥ 2 hypocalcemia during any cycle should be administered CC-90009 in the inpatient setting for subsequent cycles (an exception can be made for subjects with grade 2 hypocalcemia lasting less than 24 hours that recovers without IV calcium [eg, calcium gluconate or calcium chloride] after discussion with the Celgene medical monitor).

[f] Multiple measurements performed on this day. For subjects who are administered as in-patient in Cycles ≥ 2, on days that CC-90009 is administered, vital signs will be obtained prior to dosing (≤ 3 hours), and 60 minutes (± 15 minutes) and 6 hours (± 1 hr) after the end of the administration of the dose. Starting in Cycle 2 in the outpatient setting, vital signs will be obtained prior to dosing (≤ 3 hours) and at 60 minutes (± 15 minutes) after the end of the administration of the dose. Additional vital signs should be obtained as clinically indicated per the Investigator's medical assessment.

[g] Triplicate ECGs will be performed on Day 1 of each cycle (refer to Section 6.2.5) and a single ECG obtained at the EOT visit.

[h] The EOT Visit LVEF is not required if the prior LVEF was performed within 56 days.

[i] Per the PPP, a pregnancy test is required 28 days after the last dose of for all FCBP. For FCBP with irregular menstrual periods, a pregnancy test is required every 14 days (ie, Day 15 of Cycles ≥ 2 and at 14 and 28 days after the last dose of CC-90009).

[j] In the event of Grade ≥ 2 hypocalcemia or symptoms of hypocalcemia (eg, carpopedal spasm, tetany, seizures, etc), subjects must be hospitalized. Also, if Grade ≥ 2 hypocalcemia and abnormal levels of serum albumin occurs, a serum ionized calcium test must be performed. Refer to Section 7.2.13.2 for hypocalcemia management guidelines. Refer to Section 6.2.8 for required days and timing of tests. Subjects who experienced Grade ≥ 2 hypocalcemia during Cycle 1, require testing Days 1-7 at 6 and 12 hours postdose. All other subjects require testing prior to dosing.

[k] If intra-subject dose escalation occurs, blood samples for PD assays will be collected during the first cycle only at the increased dose; see laboratory manual for details. Multiple blood samples will be collected for this assay on the specified Days 1, 2, 5. Refer to Section 6.6.

[l] Bone marrow samples for biomarker PD assessment are mandatory. When applicable (refer to time points in the table above), bone marrow samples for biomarker PD assessment will be obtained at the same time as a scheduled efficacy assessment. If sufficient bone marrow aspirate specimen is not available, peripheral blood may be submitted in place of the BMA specimen for biomarker studies (eg, MRD); see laboratory manual for details. A bone marrow biopsy can be collected in conjunction with an aspirate if it is standard institutional practice. A bone marrow biopsy must be collected if adequate aspirate sample is not attainable; see for details on sending samples to the central laboratory for disease assessment.

[m] If end of Cycle 2 (Day 28 ± 3 days) samples are obtained on Day 1 of Cycle 3, they must be obtained prior to CC-90009 administration. Additionally, bone marrow aspirates and biopsies may be obtained after a CR is confirmed, if relapse is suspected, or following treatment discontinuation to elucidate effects of long-term treatment or resistance mechanisms. Additional aspirates and biopsies will be collected as clinically indicated based on the Investigator's medical assessment.

[n] For subjects that complete dosing in Cycle 4, performed/obtained once on Day 28 (± 3 days). For subjects that continue (after consultation with Medical Monitor) beyond Cycle 4, efficacy and bone marrow PD assessments may be obtained to confirm a CR, if relapse is suspected, or following treatment discontinuation to elucidate effects of long-term treatment or resistance mechanisms. Additional aspirates and biopsies will be collected as clinically indicated based on the Investigator's medical assessment. Refer to Section 6.3.2 and Section 6.4.

[o] Predose blood sample for both intensive and sparse sampling schedule in Cycles 2-4. Refer to Sections 6.5 and 6.6.

[p] Serum will be collected approximately every 6 months during study treatment and at EOT to be used for possible measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG). Serum should also be collected approximately 4 weeks after a documented or suspected SARS-CoV-2 infection.

Appendix O: Part A Table of Events for D1-10 Dosing Schedule

Table 37: Table of Events for Part A (D1-10 Schedule) of Cycle 1

	Screening	Treatment Period														
		Cycle 1														
		WK1							WK2			WK3	WK4		WK5[b]	WK6[b]
Events[a]	**D-28 to -1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D15**	**D22**	**D28[c]**	**D29**	**D36**
Study Entry (Section 6.1)																
Informed consent	X															
Inclusion/ exclusion criteria	X															
Medical/ oncologic history	X															
Demographics	X															
IRT registration	X	X														
Pregnancy risk counseling and contraceptive compliance confirmation	X	As specified in Section 6.1.1 and the PPP in Appendix L														
Prior/ concomitant medications & procedures (Section 6.2.1)	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
CC-90009 Administration (Section 7)																
Calcium, calcitriol, and vitamin D supplements and recording on diary card (refer to Section 7.2)	X (D-3 to D-1)	X	X	X	X	X	X	X	X	X	X[d]			X[d]		X[d]
Provide/ review diary card	X	X														
Corticosteroid administration (dexamethasone) (refer to Section 7.2) for doses 3.0 mg and above		X	X	X	X	X	X	X	X	X	X					
IV administration of CC-90009[e]		X	X	X	X	X	X	X	X	X	X					
Monitoring as inpatient		X	X	X	X	X	X	X	X	X	X					
Safety Assessments (Section 6)																
Adverse Event Evaluation (Section 6.2.2)	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Height	X															

Table 37: Table of Events for Part A (D1-10 Schedule) of Cycle 1

Events[a]	Screening	Treatment Period														
		Cycle 1														
		WK1							WK2			WK3	WK4		WK5[b]	WK6[b]
	D-28 to -1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D15	D22	D28[c]	D29	D36
Weight (Section 6.2.3)	X	X							X			X	X			
Vital Signs (Section 6.2.3)	X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X	X		X	X
Physical Examination (Section 6.2.4)	X	X							X							
ECOG PS (Appendix D)	X	X							X							
12-lead ECG (in triplicate, Section 6.2.5)	X (≥72 hrs prior to D1)	X[f]							X		X[f]					
LVEF (ECHO/MUGA scan; Section 6.2.6)	X															
Pregnancy testing per PPP (FCBP only; Section 6.2.7)	X[g]								X			X	X			X
Hematology laboratory tests (Section 6.2.8)	X (D-14 to -1)	X	X	X	X	X	X	X	X	X	X	X	X		X	X
G6PD (Section 6.2.8)	X															
Serum chemistry laboratory tests (Section 6.2.8)[h]	X (D-3 to -1)	X[i]	X[i]	X[i]	X	X	X	X	X	X	X	X	X		X	X
Additional serum Ca, Mg and PTH tests (Section 6.2.8)[h]		X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]					
Serum PTH, P1NP, β-CTx tests (Section 6.2.8)		X							X			X	X			
Serum 25-hydroxyvitamin D level (Section 6.2.8)	X	X														
Urine Ca/ creatinine ratio (random) (Section 6.2.8)		X							X			X	X			

Table 37: Table of Events for Part A (D1-10 Schedule) of Cycle 1

Events[a]	Screening	Treatment Period														
		Cycle 1														
		WK1							WK2			WK3	WK4		WK5[b]	WK6[b]
	D-28 to -1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D15	D22	D28[c]	D29	D36
Amylase, lipase, T-cell subsets (CD4+ and CD8+), TSH (Section 6.2.8)		X														
PT, INR, PTT (Section 6.2.8)[k]	X															
Urinalysis (Section 6.2.8)	X (D-14 to -1)											X				
PK & PD Assessments																
Blood, PK (Section 6.5)		X[l]	X	X[l]	X						X[l]					
Urine, PK (Section 6.5) selected subjects[r]		X														
Pharmacogenomics sample (eg, buccal cells or nail clippings), (Section 6.6.1)		X														
Blood (whole), biomarker flow cytometry (Section 6.6.2)	X (D-14 to -1)	X[l]	X[l]	X[l]					X			X				
Blood (PBMCs), PD protein and RNA (Section 6.6.2)	X (D-14 to -1)	X[l]	X	X					X							
Blood (PBMCs), PD ex vivo sensitivity assays, phenotyping & sequencing (Section 6.6.2)		X														
Blood (plasma), PD cytokines (Section 6.6.2)	X (D-14 to -1)	X	X	X	X				X							
Bone marrow aspirate and biopsy, PD biomarkers & MRD (Section 6.6.3)[m]	X (D-14 to -1)										X[n]			X (± 3d)		

Table 37: Table of Events for Part A (D1-10 Schedule) of Cycle 1

	Screening	Treatment Period														
		Cycle 1														
		WK1							WK2			WK3	WK4		WK5[b]	WK6[b]
Events[a]	D-28 to -1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D15	D22	D28[c]	D29	D36
Efficacy																
Bone marrow aspiration and biopsy, complete blood counts and examination of peripheral blood smears (Section 6.4)[o]	X (D-14 to -1)[p]													X (± 3d)		X (only on D42 ± 3d)[q]

Abbreviations: β-CTx = beta C-terminal telopeptide; C = cycle; Ca = calcium; CD = cluster of differentiation; D = day; ECHO = echocardiogram; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FCBP = females of child bearing potential; G6PD = glucose-6-phosphate dehydrogenase; hrs = hours; INR = international normalized ratio; IRT = integrated response technology; IV = intravenous; LVEF = left ventricular ejection fraction; Mg = magnesium; MRD = Minimal Residual Disease; MUGA = multi-gated acquisition scan; P1NP = procollagen type 1 N-terminal propeptide; PBMC = peripheral blood mononuclear cells; PD = pharmacodynamic; PK = pharmacokinetic; PPP = pregnancy prevention plan; PT = prothrombin time; PTH = parathyroid hormone; PTT = partial thromboplastin time; RNA = ribonucleic acid; TSH = thyroid-stimulating hormone; WK = week.

[a] All study visits/procedures will have a ± 2 day window and all laboratory blood samples should be drawn predose (≤ 5 hrs), unless otherwise specified in this table or Section 6.

[b] Subjects with hypoplastic bone marrow without evidence of persistent AML at the Day 28 assessment who have Grade ≥ 3 neutropenia will be followed for an additional 2 weeks for safety monitoring in Cycle 1 (total duration of 42 days; refer to Figure 1). Not all visits are shown as separate columns under Week 6, ie, Day 42 bone marrow assessment.

[c] Eligible subjects continue on to Cycle 2 (refer to Table 5). Based on the Day 28 bone marrow evaluation, subjects with a hypoplastic bone marrow without evidence of persistent leukemia who have Grade ≥ 3 neutropenia will be followed for an additional 2 weeks for safety monitoring in Cycle 1.

[d] Supplementation may be prolonged if hypocalcemia occurs (refer to Section 7.2.13.2). Subjects are to start supplements at least 3 days prior to Day 1 of Cycle 2 as per Section 7.2.

[e] Subjects will be closely monitored during administration of CC-90009 and for at least one hour after. Subjects should be adequately hydrated to prevent potential tumor lysis syndrome (TLS) (eg, 2 to 3 liters of oral or IV fluids per day) starting the day prior to CC-90009 administration and continuing through each day of CC-90009 administration. Refer to Section 7.2.12 for information on dose interruptions. The SRC may decide to evaluate alternate dosing schedules (eg, increasing from 5 to up to 10 consecutive days of CC-90009 administration) based on their review of available clinical and laboratory safety data, PK profiles, and PD findings.

[f] Multiple measurements performed on this day.

[g] Two pregnancy tests (sensitivity of at least 25 mIU/mL) must be performed prior to first dose of CC-90009: within 10 to 14 days prior and within 24 hours prior. Both tests must be negative for CC-90009 dosing to begin.

[h] A free (ionized) serum calcium test should be obtained at Screening to establish baseline values in addition to the corrected serum calcium test (corrected for albumin) used to fulfill the inclusion criteria. In the event of Grade ≥ 2 hypocalcemia or symptoms of hypocalcemia (eg, carpopedal spasm, tetany, seizures, etc), subjects must be hospitalized. Also, if Grade ≥ 2 hypocalcemia and abnormal levels of serum albumin occurs, a serum ionized calcium test must be performed. Refer to Section 7.2.13.2 for hypocalcemia management guidelines.

[i] Specific tests for TLS monitoring required predose and 12 hours (± 1 hour) postdose on Days 1, 2, and 3. Refer to Section 6.2.8.

[j] Additional serum calcium/magnesium tests required 6 and 12 hours (± 1 hour) postdose on days of CC-90009 administration. Additional PTH tests required at 6 hours (± 1 hours) post-dose on days of CC-90009 administration.

[k] Subsequent coagulation tests only performed for subjects on anticoagulant therapy and as clinically indicated.

[l] Multiple blood samples will be collected for this assay on the specified day. Refer to Sections 6.5 and 6.6.

[m] Bone marrow samples for biomarker assessment are mandatory. If bone marrow samples are scheduled to be collected on the same day for efficacy, the biomarker samples should be collected at the same time. If sufficient bone marrow aspirate specimen is not available, peripheral blood may be submitted in place of the BMA specimen for biomarker studies (eg, MRD); see laboratory manual for details.

[n] Obtained between 4 to 8 hours postdose. The samples may be obtained on Day 6 or Day 8 if necessary due to scheduling difficulties. If the dosing interval (schedule) is extended, then samples will be obtained on the last day ±1 day of dosing (eg, if extended to 10 day, obtain on Day 9-11).

[o] Additional aspirates and biopsies will be collected as clinically indicated (eg, Cycle 1 Day 15 based on Investigator's medical assessment).

[p] Molecular and cytogenetic studies may be omitted at: Screening, if they were completed within the previous 90 days and the results are available for recording on the electronic case report forms and Day 42 (or at hematologic recovery), if a complete response is documented at Day 28.

[q] Additional bone marrow assessment performed at the time of hematologic recovery or Day 42 (± 3 days). Eligible subjects continue on to Cycle 2 (refer to Table 5).

[r] Urine PK to be performed on approximately 10 selected subjects from Part A and/or Part B. This is a 24-hour collection that starts on C1D1 and ends on C1D2.

Table 38: Table of Events for Part A (D1-10 Schedule) of Cycles ≥ 2

Events[a]	Treatment Period														Follow-up Period	
	Cycles ≥ 2													EOT[b]	Safety[c]	Long Term
	WK1							WK2			WK3	WK4				
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D15	D22	D28	≤ 28 days	28 days (± 3 days)	
Review concomitant medications & procedures (Section 6.2.1)	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
CC-90009 Administration (Section 7)																
Calcium, calcitriol and Vitamin D supplements and recording on diary card (Section 7.2)	X	X	X	X	X	X	X	X	X	X[d]			X (C2 and C3)[d]			
Provide/ review of diary card	X													X		
Corticosteroid administration (dexamethasone) (refer to Section 7.2) for doses 3.0 mg and above	X	X	X	X	X	X	X	X	X	X						
IV administration of CC-90009[e]	X	X	X	X	X	X	X	X	X	X						
Safety Assessments (Section 6)																
Adverse Event Evaluation (Section 6.2.2)	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Weight (Section 6.2.3)	X													X		
Vital Signs (Section 6.2.3)	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X	X		X		
Physical Examination (Section 6.2.4)	X													X		
ECOG PS (Appendix D)	X													X		
12-lead ECG (Section 6.2.5)[g]	X													X		
LVEF (ECHO/MUGA; Section 6.2.6)	X (only C2 ± 7d)													X (± 7d)h		

Table 38: Table of Events for Part A (D1-10 Schedule) of Cycles ≥ 2

	Treatment Period														Follow-up Period	
	Cycles ≥ 2															
	WK1							WK2			WK3	WK4		EOT[b]	Safety[c]	
Events[a]	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D15	D22	D28	≤ 28 days	28 days (± 3 days)	Long Term
Pregnancy test (FCBP only; Section 6.2.7)	X										X[i]			Xi	Xi	
Pregnancy risk counseling and contraceptive compliance confirmation	X	As specified in Section 6.1.1 and the PPP in Appendix L														
Hematology laboratory (Section 6.2.8)	X	X	X	X	X	X	X	X	X	X	X	X		X		
Serum chemistry laboratory tests (Section 6.2.8)[j]	X	X						X			X	X		X		
Serum Ca & Mg tests (Section 6.2.8)[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]						
Serum PTH, P1NP, β-CTx tests (Section 6.2.8)	X									X				X		
Serum 25-hydroxyvitamin D level (Section 6.2.8)	X															
Urine Ca/ creatinine ratio test (random) (Section 6.2.8)	X									X				X		
Amylase, lipase, T-cell subsets (CD4+ and CD8+), TSH (Section 6.2.8)	X													X		
PT, INR, PTT (for subjects on anticoagulant therapy) (Section 6.2.8)	X													X		
Urinalysis (Section 6.2.8)	X													X		
PK & PD Assessments																
Blood, PK (Section 6.5)[o]	X	X	X	X						X[o]						

Table 38: Table of Events for Part A (D1-10 Schedule) of Cycles ≥ 2

Events[a]	Treatment Period													EOT[b]	Follow-up Period	
	Cycles ≥ 2														Safety[c]	
	WK1							WK2			WK3	WK4				
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D15	D22	D28	≤ 28 days	28 days (± 3 days)	Long Term
Blood (whole), biomarker flow cytometry, (Section 6.6.2) first cycle of intra-subject dose escalation only[k]	X[k]	X[k]	X[k]					X[k]			X[k]					
Blood (PBMCs), PD protein and RNA (Section 6.6.2) first cycle of intra-subject dose escalation only[k]	X[k]	X[k]	X[k]					X[k]								
Blood (plasma), PD cytokines (Section 6.6.2) first cycle of intra-subject dose escalation only[k]	X	X	X	X				X								
Bone marrow aspirate and biopsy, PD biomarkers & MRD (Section 6.6.3)[l, m]													X (C2 and C4; ± 3d)	Xn		Refer to Section 6.3.2
Efficacy																
Complete blood counts and examination of peripheral blood smears (Section 6.4)[m]													X (C2 and C4; ± 3d)	X[n]		Refer to Section 6.3.2
Bone marrow aspirate and biopsy (Section 6.4)[m]													X (C2 and C4; ± 3d)	X[n]		Refer to Section 6.3.2
Follow-up																
CC-90009-related AE/SAE follow-up	Refer to Section 6.3.1															
Anticancer therapies	Refer to Section 6.3.2															
Survival	Refer to Section 6.3.3															

Abbreviations: Adverse event = AE; β-CTx = beta C-terminal telopeptide; C = cycle; Ca = calcium; CD = cluster of differentiation; D = day; ECHO = echocardiogram; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; FCBP = females of child bearing potential; INR = international normalized ratio; IV = intravenous; LVEF = left ventricular ejection fraction; Mg = magnesium; MUGA = multi-gated acquisition scan; P1NP = procollagen type 1 N-terminal propeptide; PD = pharmacodynamics; PPP = pregnancy prevention plan; PT = prothrombin time; PTH = parathyroid hormone; PTT = partial thromboplastin time; q = every; SAE = serious adverse event; TSH = thyroid-stimulating hormone; WK = week.

[a] All study visits/procedures will have a ± 2 day window and all laboratory blood samples should be drawn predose (≤ 5 hrs), unless otherwise specified in this table or Section 6. Cycles should start ≤ 7 days after the last day of the previous cycle.

[b] EOT Visit performed within 28 days after last dose of CC-90009 for subjects that discontinue prior to completing dosing in Cycle 4. For subjects that complete dosing in Cycle 4, this visit should be completed on Day 28 (± 2 days) of Cycle 4. For subjects who complete dosing after Cycle 4, EOT Visit should be completed within 28 days after the last day of the previous cycle.

[c] Safety Follow-up Visit is performed 28 days (± 3 days) after the last dose of CC-90009 for all subjects. May be performed by telephone contact if pregnancy testing is not required (refer to footnote "i").

[d] Supplements to be administered for at least 3 days after the last dose in each cycle. Supplementation may be prolonged if hypocalcemia occurs (refer to Section 7.2.13.2). Subjects to start supplements at least 3 days prior to Day 1 of Cycles 3 and 4 as per Section 7.2.

[e] Subjects will be closely monitored during the administration of CC-90009 and for at least 1 hour after. Subjects should be adequately hydrated to prevent potential tumor lysis syndrome (TLS) (eg, 2 to 3 liters of oral or IV fluids per day) starting the day prior to CC-90009 administration and continuing through each day of CC-90009 administration. Refer to Section 7.2.12 for information on dose interruptions. The SRC may decide to evaluate alternate dosing schedules (eg, increasing from 5 to up to 10 consecutive days of CC-90009 administration) based on their review of available clinical and laboratory safety data, PK profiles, and PD findings. Subjects should be administered Cycle ≥ 2 of CC-90009 in a Limited Stay Unit (LSU) or as in patient. Subjects experiencing Grade ≥ 2 hypocalcemia during any cycle should be administered CC-90009 in the inpatient setting for subsequent cycles (an exception can be made for subjects with grade 2 hypocalcemia lasting less than 24 hours that recovers without IV calcium [eg, calcium gluconate or calcium chloride] after discussion with the Celgene medical monitor).

[f] Multiple measurements performed on this day.

[g] Triplicate ECGs will be performed on Day 1 of each cycle (refer to Section 6.2.5) and a single ECG obtained at the EOT visit.

[h] The EOT Visit LVEF is not required if the prior LVEF was performed within 56 days.

[I] Per the PPP, a pregnancy test is required 28 days after the last dose of for all FCBP. For FCBP with irregular menstrual periods, a pregnancy test is required every 14 days (ie, Day 15 of Cycles ≥ 2 and at 14 and 28 days after the last dose of CC-90009).

[j] In the event of Grade ≥ 2 hypocalcemia or symptoms of hypocalcemia (eg, carpopedal spasm, tetany, seizures, etc), subjects must be hospitalized. Also, if Grade ≥ 2 hypocalcemia and abnormal levels of serum albumin occurs, a serum ionized calcium test must be performed. Refer to Section 7.2.13.2 for hypocalcemia management guidelines. Refer to Section 6.2.8 for required days and timing of tests. Subjects who experienced Grade ≥ 2 hypocalcemia during Cycle 1, require testing Days 1-7 at 6 and 12 hours postdose. All other subjects require testing prior to dosing. If intra-subject dose escalation occurs, subjects should be treated as in Cycle 1.

[k] If intra-subject dose escalation occurs, blood samples for PD assays will be collected during the first cycle only at the increased dose; see laboratory manual for details. Multiple blood samples will be collected for this assay on the specified Days 1, 2, 3. Refer to Section 6.6.

[l] Bone marrow samples for biomarker PD assessment are mandatory. When applicable (refer to time points in the table above), bone marrow samples for biomarker PD assessment will be obtained at the same time as a scheduled efficacy assessment. If sufficient bone marrow aspirate specimen is not available, peripheral blood may be submitted in place of the BMA specimen for biomarker studies (eg, MRD); see laboratory manual for details.

[m] If end of Cycle 2 (Day 28 ± 3 days) samples are obtained on Day 1 of Cycle 3, they must be obtained prior to CC-90009 administration. Additionally, bone marrow aspirates and biopsies may be obtained in both Part A and Part B, after a CR is confirmed, if relapse is suspected, or following treatment discontinuation to elucidate effects of long-term treatment or resistance mechanisms. Additional aspirates and biopsies will be collected as clinically indicated based on the Investigator's medical assessment.

[n] For subjects that complete dosing in Cycle 4, performed/obtained once on Day 28 (± 3 days). For subjects that continue (after consultation with Medical Monitor) beyond Cycle 4, efficacy and bone marrow PD assessments may be obtained to confirm a CR, if relapse is suspected, or following treatment discontinuation to elucidate effects of long-term treatment or resistance mechanisms. Additional aspirates and biopsies will be collected as clinically indicated based on the Investigator's medical assessment. Refer to Section 6.3.2 and Section 6.4.

- Blood samples for PK are to be collected in Cycle 2 only; on Day 7 there is a pre-dose and 24 hour postdose sample Section 6.5.1.

Appendix P: The Operating Characteristics of the Proposed Bayesian Safety Monitoring Plan

The enrollment may stop to ensure the posterior probability of excess AE rate exceeding 25% is not more than 70%, ie, when:

- Prob (rate of AEs that fulfill DLT criteria or treatment related AEs leading to dose reduction or discontinuation or rate of sepsis >0.25|data, a, b) > 0.70.

Where a, b are parameters of Beta distribution. Weakly informative priors, ie, beta (0.5, 0.5), may be used for the posterior probability calculations. The excess toxicity of 25% is established based on the inputs from clinical with threshold of 70% based on empirical data analysis.

Table 39 below shows the simulation results of the probability to stop further enrollment based on above condition with various true toxicity rate.

Table 39: The Operating Characteristics for Bayesian Monitor Plan

	The True Toxicity Rate								
Number of Subjects	**Number Of Subjects with AEs That Fulfill DLT Criteria or Treatment Related AEs Leading to Treatment Reduction or Discontinuation or AEs of Sepsis for Stop**	**0.1**	**0.15**	**0.2**	**0.25**	**0.3**	**0.35**	**0.4**	**0.45**
8	3	3.8%	10.5%	20.3%	32.2%	44.8%	57.2%	68.5%	78.0%
10	4	5.3%	14.1%	26.2%	39.9%	53.7%	66.3%	76.8%	85.1%
13	5	5.8%	15.8%	29.6%	45.0%	59.9%	72.8%	82.9%	90.1%
17	6	6.2%	17.3%	33.0%	50.4%	66.5%	79.5%	88.7%	94.4%
21	7	6.4%	18.3%	35.6%	54.5%	71.5%	84.2%	92.3%	96.8%
24	8	6.4%	18.7%	36.6%	56.3%	73.6%	86.1%	93.7%	97.6%
28	9	6.5%	19.1%	37.8%	58.5%	76.4%	88.6%	95.4%	98.5%
32	10	6.5%	19.4%	38.9%	60.6%	78.8%	90.6%	96.6%	99.0%
35	11	6.5%	19.5%	39.4%	61.5%	79.9%	91.5%	97.2%	99.3%
39	12	6.5%	19.6%	40.0%	62.9%	81.5%	92.8%	97.8%	99.5%

Note: Only unique stopping boundaries are presented up to the estimated maximum enrollment of 40 subjects in an expansion cohort.

Appendix Q: Blood Collection for PK Analysis

Table 40: Blood Pharmacokinetic Sampling Schedule for Cycle 1 in Part A for D1-5 and Alternative Schedules with up to 10 consecutive dosing days (eg, D1-7 and D1-10)

Time Relative to CC-90009 Administration	Collection Window	Day 1	Day 3	Day 4	Cycle 1 Last Dose[a]
0	≤ 30 minutes prior to start	X	X	X	X
Mid-infusion (eg, at 15 minutes in a 30 minute infusion)[b]	± 1 minute	X			X
15 minutes after EOI	± 5 minutes	X			X
30 minutes after EOI	± 5 minutes	X			X
1 hour after EOI	± 5 minutes	X	X		X
2 hours after EOI	± 10 minutes	X			X
4 hours after EOI	± 10 minutes	X	X		X
8 hours after EOI	± 30 minutes	X			X
12 hours after EOI	± 2 hours	X			
24 hours after EOI	± 3 hours	X[c]			X

EOI = end of infusion/injection.

[a] Day of last dose in a schedule with up to 10 consecutive days of CC-90009 dosing. On the D1-5 schedule, PK will be collected on Cycle 1 Day 5. On the D1-7 schedule, PK will be collected on Cycle 1 Day 7. On the D1-10 schedule, PK will be collected on Cycle 1 Day 10. If a dosing schedule with less than 5 days is tested, the intensive PK samples for the last dosing day will not be collected.

[b] In cases where the only access for drug administration is the central line, mid-infusion PK draws may be omitted.

[c] 24 hours after EOI on Day 1 occurs on Day 2. Must be drawn prior to the administration of CC-90009 on Day 2.

Table 41: Blood Pharmacokinetic Sampling Schedule for Cycle 2 in Part A for D1-5 and Alternative Schedules with up to 10 consecutive dosing days (eg, D1-7 and D1-10)

Time Relative to CC-90009 Administration	Collection Window	Day 1	Day 2	Day 3	Day 4	Cycle 2 Last Dose[a]
0	≤ 30 minutes prior to start		X	X	X	X
Mid-infusion (eg, at 15 minutes in a 30 minute infusion)[b]	± 1 minutes	X				X
24 hours after EOI	± 3 hours					X

EOI = end of infusion/injection.

[a] Day of last dose in a schedule with up to 10 consecutive days of CC-90009 dosing. If it's a D1-5 schedule, PK will be collected on Cycle 2 Day 5. If it's a D1-7 schedule, PK will be collected on Cycle 2 Day 7. If it's a D1-10 schedule, PK will be collected on Cycle 2 Day 10. If dosing is not scheduled for Cycle 2 last dosing day, last dosing day PK will not be collected.

[b] In cases where the only access for drug administration is the central line, mid-infusion PK draws may be omitted.

Table 42: Blood Pharmacokinetic Sampling Schedule for Cycle 1 in Part A for D1-3/D8-10 Schedule

Time Relative to CC-90009 Administration	Collection Window	Day 1	Day 3	Day 8	Day 10
0	≤ 30 minutes prior to start	X	X	X	X
Mid-infusion (eg, at 15 minutes in a 30 minute infusion)[a]	± 1 minute	X		X	
15 minutes after EOI	± 5 minutes	X		X	
30 minutes after EOI	± 5 minutes	X		X	
1 hour after EOI	± 5 minutes	X	X	X	
2 hours after EOI	± 10 minutes	X		X	
4 hours after EOI	± 10 minutes	X	X	X	
8 hours after EOI	± 30 minutes	X		X	
12 hours after EOI	± 2 hours	X			
24 hours after EOI	± 3 hours	X[b]	X[b]	X[b]	X[b]

EOI = end of infusion/injection.

[a] In cases where the only access for drug administration is the central line, mid-infusion PK draws may be omitted.

[b] 24 hours after EOI on day 1 occurs on Day 2; 24 hours after Day 3 occurs on Day 4; 24 hours after Day 8 occurs on Day 9; 24 hours after Day 10 occurs on Day 11. Must be drawn prior to the administration of CC-90009 on Day 2 and Day 9.

Table 43: Blood Pharmacokinetic Sampling Schedule for Cycle 2 in Part A for D1-3/D8-10 Schedule

Time Relative to CC-90009 Administration	Collection Window	Day 1	Day 3	Day 8	Day 10
0	≤ 30 minutes prior to start		X		X
Mid-infusion (eg, at 15 minutes in a 30 minute infusion)[a]	± 1 minutes	X		X	X
24 hours after EOI	± 3 hours	X[b]	X[b]	X[b]	X[b]

EOI = end of infusion/injection.

[a] In cases where the only access for drug administration is the central line, mid-infusion PK draws may be omitted.

[b] 24 hours after EOI on day 1 occurs on Day 2; 24 hours after Day 3 occurs on Day 4; 24 hours after Day 8 occurs on Day 9; 24 hours after Day 10 occurs on Day 11. Must be drawn prior to the administration of CC-90009 on Day 2 and Day 9.

Table 44: Blood Pharmacokinetic Sampling Schedule in Part B: 3.6 mg Day 1-5 Schedule

Time Relative to CC-90009 Administration	Collection Window	Intensive	Sparse
Cycle 1 Day 1			
0	≤ 30 minutes prior to start	X	
Mid-infusion (eg, at 15 minutes in a 30 minute infusion)[a]	± 1 minute	X	
15 minutes after EOI	± 5 minutes	X	
30 minutes after EOI	± 5 minutes	X	X
1 hour after EOI	± 5 minutes	X	X
2 hours after EOI	± 10 minutes	X	
4 hours after EOI	± 10 minutes	X	X
8 hours after EOI	± 30 minutes	X	
12 hours after EOI	± 2 hours	X	
24 hours after EOI	± 3 hours	X[b]	X[b]
Cycles 2-4			
Second to last dosing day, pre-dose	≤ 30 minutes prior to start	X	X
Last dosing day, pre-dose	≤ 30 minutes prior to start	X	X

EOI = end of infusion/injection.

[a] In cases where the only access for drug administration is the central line, mid-infusion PK draws may be omitted.

[b] 24 hours after EOI on day 1 occurs on Day 2. Must be drawn prior to the administration of CC-90009 on Day 2.